BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL

Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk . . . . ✍

Dear friends and colleagues,

I am extremely pleased to release the first issue of bulletin on Adverse drug reaction of the year 2019.

There is an increased incidence of cancer globally, therefore path breaking research is going on in this field. One of the challenges with use of anticancer agents is the management of their adverse effects. Chemotherapy induced nausea and vomiting (CINV) is one such common ADR encountered which may interfere with treatment outcome. Hence drugs counteracting these ADRs play an important role. The review article on CINV will give us an overview of drugs used in this condition.

The other review article gives us an insight on a niche area of pigmentation problem induced by drugs. Apart from this, interesting case report, puzzle and tedious exercise of match the column are the main highlights of this issue.

As a result of diligent pharmacovigilance activities, we present data which is an analysis of ADRs reported in our department.

I sincerely hope that this issue enlightens the readers regarding adverse drug reactions.

Finally, I would like to thank all the clinical departments of our institute for their valued contribution to pharmacovigilance and to the authors for contributing in the bulletin. I would also like to thank all the members of department of pharmacology for their hard work in unfolding our current issue of this bulletin.

Thank you,

Dr. Sudhir Pawar

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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Introduction[1,2]

Cancer is one of the leading causes of morbidity and mortality worldwide. In India about 6% of all deaths are due to cancers, which contribute to 8% of global cancer mortality.[3] Advances in the understanding of the pathophysiology of cancer, has led to the development of newer therapies like molecular targeted therapy, immunotherapy and gene therapy. But still chemotherapy is the mainstay of the treatment for advanced malignant diseases. Though chemotherapy improves survival, it has its own toxicity and side effects. The most common of side effects are alopecia, nausea and vomiting, mucositis, and myelosuppression of which Chemotherapy-induced nausea and vomiting (CINV) is the most common and intolerable adverse event. To date, between 13% to 60% of oncology patients experience CINV. CINV can lead to number of complications like oesophageal tears, metabolic imbalance, lowered cognitive function, and increased anxiety or depression which can worsen the patient's condition. In the past CINV forced up to 20% of patients to postpone or refuse potentially curative treatment.[4] Poorly controlled or severe CINV can prompt reduction in a chemotherapy dose or delay in chemotherapy cycles, ultimately affecting chemotherapy outcomes hence it is ideal to prevent nausea and vomiting but once it occurs, every effort should be made to eliminate it, or at least to minimize it. The goal of prophylaxis should be to reduce the morbidity associated with nausea and vomiting, and to preserve quality of life, while continuing the optimum chemotherapy regimen.

Pathophysiology of CINV[5]

CINV is a very complex condition which involves both the central and the peripheral nervous system (see Figure 1). Chemotherapy causes the release of various neurotransmitters in the gastrointestinal tract, cerebral cortex and thalamus, vestibular region and area postrema. These neurotransmitters include dopamine, endorphin, serotonin and substance P. The acute phase of vomiting is mainly mediated by serotonin from enterochromaffin cells located in the intestinal mucosa. This serotonin then binds to 5-hydroxytryptamine 3 (5-HT3) receptors located on vagal afferent nerves in the intestinal wall, which sends signals to the vomiting centre in the medulla via the chemoreceptor trigger zone in the area postrema. The delayed phase of CINV is mainly associated with central pathway located in the brain. In addition, chemotherapy also triggers the production of substance P, which binds to NK1 receptors in neural networks, which mediates the induction of emesis. NK1 receptors are also located on vagal afferent terminals in the gastrointestinal tract, suggesting the release of substance P from enterochromaffin cells following chemotherapy which might be associated in the acute phase of CINV. Both pathways should be blocked to optimise CINV control. The peripheral pathway is primarily responsible for acute CINV, while the central pathway controls delayed CINV. Antagonists of 5-HT3 and NK1 receptors have therefore been developed as antiemetic agents.

Classification of CINV

- Acute CINV: Vomiting occurs within a few minutes to several hours after administration of chemotherapy agent and usually peaking in the first 4-6 hours

- Delayed CINV: Onset of emesis more than 24 hours after administration of chemotherapy agent

- Anticipatory CINV: When emesis occurs prior to chemotherapy administration as a conditioned response in patients who have experienced emesis during a previous cycle of chemotherapy it called as anticipatory CINV

- Breakthrough/refractory CINV: Emesis despite prophylactic medications

Figure 1. Pathways by which chemotherapeutic agents produces nausea and vomiting[5]
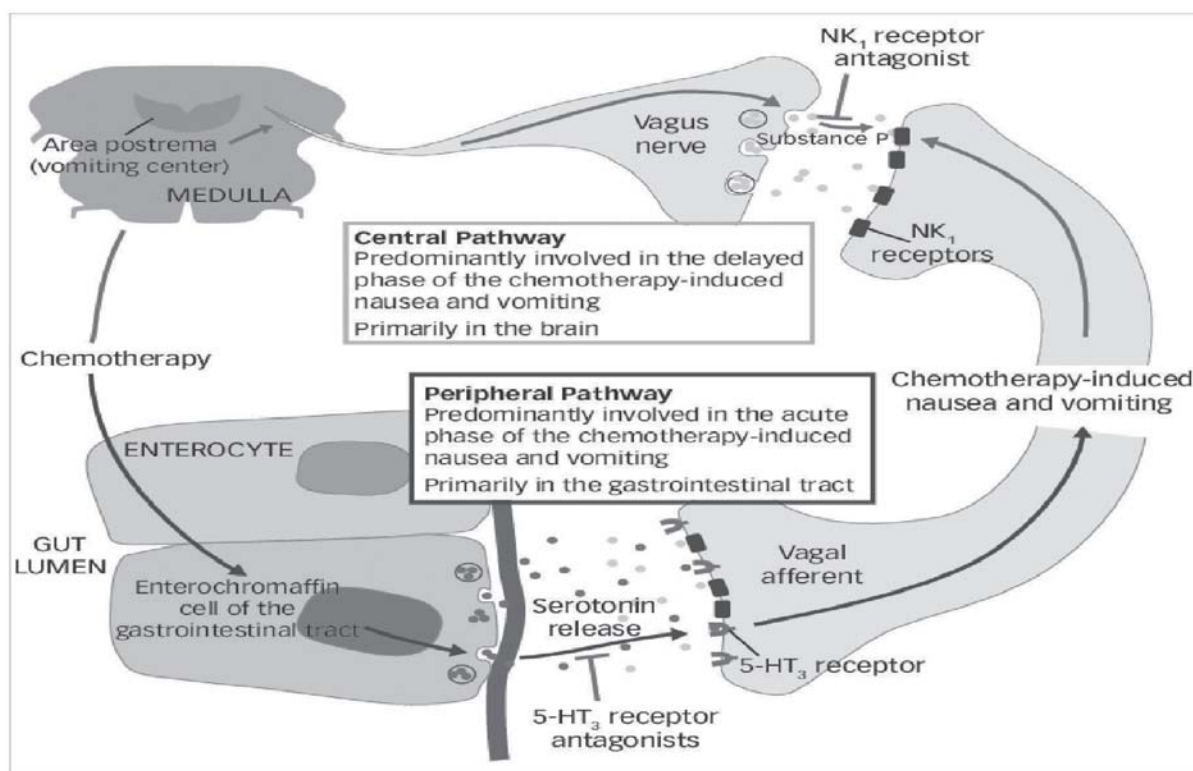
Chemotherapy regimens are classified as following risk groups[2]

- Regimens with **High** emetic risk: ≥90% or more of patients experience emesis.
  E.g. Anthracycline/cyclophosphamide (AC) combination, carmustine, cisplatin, cyclophosphamide >1,500 mg/m^2, facarbazine etc.

- Regimens with **Moderate** emetic risk: 30% to 90% of patients experience emesis.
  E.g. Alemtuzumab, bendamustine, busulfan, carboplatin, idarubicin, ifosfamide, irinotecan etc.

- Regimens with **Low** emetic risk: 10% to 30% of patients experience emesis.
  E.g. Bortezomib, brentuximab, cabazitaxel, carfilzomib, catumaxomab, cetuximab, etoposide, fluorouracil, gemcitabine, ipilimumab, methotrexate etc.

- Regimens with **Minimal** emetic risk: < 10% of patients experience emesis.
  E.g. Bevacizumab, bleomycin, 2-chlorodeoxyadenosine, cladribine, daratumumab, fludarabine, rituximab, trastuzumab, vinblastine, vincristine, vinorelbine etc.

Patient related risk factors for CINV[4]

Patients with following risk factors are at increased risk of developing nausea and vomiting during chemotherapy sessions

- Experience of nausea and/or vomiting during previous chemotherapy
- Age <50 years
- Female gender
- Anxiety
- Pre-treatment nausea
- Fatigue
- Chemotherapy adminstration on outpatient basis
- Low intake of alcohol - studies have shown that chronic alcohol intake is associated with better control of CINV because chronic alcohol intake decreases the sensitivity of CTZ.
- Impaired quality of life
- History of motion sickness
- Pain
- Vomiting during pregnancy

The guidelines to prevent CINV includes the American Society of Clinical Oncology (ASCO), the Multinational Association for Supportive Care in Cancer (MASCC) and National Comprehensive Cancer Network (NCCN). [4,5]

General recommendations for prevention are as follows:[5,6,7]

- Antiemetic drugs should be given before starting the chemotherapy regimen and should be continued for the first 24 hours
- Antiemetic agent should be selected on the basis of emetic risk of the chemotherapy regimen
- To prevent delayed emesis prophylactic treatment should be continued for 2 to 4 days following completion of chemotherapy
- In case of breakthrough/refractory emesis which is difficult to reverse, it is prevented by using routine around-the-clock administration of antiemetics, as-needed dosing is not helpful in this condition
- H2 blocker or a proton pump inhibitor can be used to prevent dyspepsia
- Other potential causes of emesis in cancer patients should also be considered (e.g., bowel obstruction)

- Prevention is also key to the management of anticipatory emesis

- Consider using lorazepam as an adjuvant to the antiemetic regimen to decrease anxiety in patients at risk for anticipatory emesis

- Non-pharmacological therapy: Relaxation/systematic desensitization, hypnosis with guided imagery, and music therapy are behavioural interventions that may be considered for anticipatory emesis; acupuncture/acupressure are additional options

Drugs used for the treatment and prevention of CINV

CINV is a complex multifactorial process involving several transmitters and receptors but the better understanding of the pathophysiology, and identification of patient risk factors, has revolutionized the prevention and treatment of CINV. With the appropriate use of evidence-based antiemetic regimens, vomiting and to a lesser extent nausea, can now be prevented in most patients. Drugs which are used for the treatment of CINV are given in the table no.1

Table 1. List of drugs used for prevention and treatment of CINV

Drug class	Drugs names
5HT3 receptor antagonist (5HT3-RA)	Ondansetron, granisetron, dolasetron, tropisetron
Neurokinin 1 receptor antagonist (NK1 RA)	Aprepitant, rolapitant, fosaprepitant, netupitant
Centrally acting Dopamine receptor antagonist	Metoclopramide
Corticosteroids	Dexamethasone, methylprednisolone
Benzodiazepine	Lorazepam, diazepam
Antipsychotics	Olanzapine

Antiemetic regimens used for prophylaxis of chemotherapy induced nausea and vomiting[1,7]

It is important to clearly define the optimal prophylactic antiemetic regimen for the prevention of acute and delayed nausea and vomiting and it should be started before initiating chemotherapy regimen because symptomatic treatment at a later stage is ineffective in most cases, especially in delayed emesis. Antiemetic regimen should be designed by taking into consideration the emetogenic potential of chemotherapy regimen.

1. **Antiemetic Prophylaxis for Prevention of Acute CINV**

   - Highly emetogenic chemotherapy

Combination therapy of 5-HT3- receptor antagonist (RA), NK-1- receptor antagonist (RA) (Aprepitant) and a corticosteroid should be given to the patient.

- Moderately emetogenic chemotherapy

Patients receiving AC chemotherapy for breast cancer should be treated with combination of a 5-HT3-RA, a NK- 1-RA (Aprepitant) and a corticosteroid. If Aprepitant is not available, then a combination of Palonosetron plus dexamethasone should be given.

Other patients receiving non AC chemotherapy should also receive a combination of the 5-HT3 RA palonosetron and dexamethasone.

- Low emetogenic chemotherapy

Patients receiving low emetogenic chemotherapy should be treated with single agent such as low dose of corticosteroid and should not be overtreated with 5-HT3-RA routinely.

- Minimally emetogenic chemotherapy

No antiemetic drug should be routinely administered before chemotherapy.

2. Prevention of Delayed CINV

The presence of delayed emesis is often underestimated, with the consequence that no adequate preventive measures are taken.

- Highly emetogenic chemotherapy

Patients are treated with combination of NK-1-RA (Aprepitant) and a corticosteroid. The addition of 5-HT3-RA is not required most of the time.

- Moderately emetogenic chemotherapy

Aprepitant or fosaprepitant should be used to prevent delayed nausea and vomiting. If patient has already taken palonosetron for acute emesis, then dexamethasone is preferred for the prevention of delayed nausea and vomiting. Multiday oral dexamethasone can also be given for prevention of delayed emesis.

Recommendations of different Guidelines [2,5,6]

Recommended antiemetic agents by emetic-risk categories are shown in the table below.

Table 2. Antiemetic treatment recommendations from different guidelines according to risk of CINV

	High risk (>90%)
NCCN recommendations	Day 1 (before chemotherapy): NK1 RA + 5-HT3 RA + DEX OR Olanzapine + palonosetron +DEX OR NK1 RA + 5-HT3 RA + DEX + olanzapine Days 2-4: Varies according to day 1 regimen

ASCO recommendations	Day 1 (before chemotherapy): NK1 RA + 5-HT3 RA + DEX + olanzapine Days 2-4: continue olanzapine on days 2-4 Add DEX on days 2-4 for high-emetic risk (non-AC)
MASCC/ ESMO recommendations	Acute: 5-HT3 RA + NK1 RA + DEX Delayed (non-AC): DEX Delayed (non-AC) if APR 125 mg has already been given for acute: Metoclopramide (MCP) + DEX or APR+ DEX Delayed (AC): None Delayed (AC) if APR 125 mg has been given for acute: DEX or APR
Moderate risk (30-90%)	
NCCN recommendations	Day 1 (before chemotherapy): 5-HT3 RA + DEX OR Olanzapine + palonosetron +DEX or NK1 RA + 5-HT3 RA + DEX Days 2-3: Varies according to day 1 regimen
ASCO recommendations	Treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min: NK1 RA + 5-HT3 RA + DEX Other moderate-risk regimens: 5-HT3 RA + DEX on day 1 Delayed: DEX on days 2-3
MASCC/ ESMO recommendations	Acute (carboplatin regimens): 5- HT3 RA + DEX+ NK1 RA Acute (excluding carboplatin based): 5-HT3 RA + DEX Delayed (carboplatin regimens): None Delayed (carboplatin regimens) if APR 125 mg for acute: APR
Low risk (10-30%)	
NCCN recommendations	Start before chemotherapy: DEX OR MCP PO/IV OR prochlorperazine or oral 5-HT3 RA
ASCO recommendations	Acute: 5-HT3 RA OR DEX
MASCC/ ESMO recommendations	Acute: DEX or 5-HT3 RA or dopamine receptor antagonist (DOP) Delayed: No routine prophylaxis
Minimal risk (<10%)	
NCCN recommendations	No routine prophylaxis
ASCO recommendations	No routine prophylaxis
MASCC/ ESMO recommendations	No routine prophylaxis

Abbreviations : *5HT3 RA - 5HT3 receptor antagonist, NK1 RA - Neurokinin 1 receptor antagonist, DEX - dexamethasone, APR - Aprepitant, MCP - Metoclopramide, AC - anthracycline and cyclophosphamide regimen, non-AC - non-anthracycline and cyclophosphamide regimen, NCCN - National Comprehensive Cancer Network, ASCO - American Society of Clinical Oncology, MASCC/ ESMO - Multinational Association for Supportive Care in Cancer/European Society for Medical Oncology*

3.   Therapy against Anticipatory Nausea and Vomiting (ANV)

ANV is a learned conditional reflex and drug therapy has modest efficacy. It can be best managed by behavioural therapies, although this may not represent an easy solution in our day to day practice. The best approach is to avoid this by using optimal antiemetic prophylaxis from the first cycle. Conventional antiemetics alone are mostly ineffective however treatment with benzodiazepines in addition to conventional antiemetic therapy has shown some efficacy if given before chemotherapy. Muscle relaxation, systemic desensitisation, hypnosis and cognitive distraction are possible interventions, but its usefulness is doubtful.

4.   Therapy in Multiple Day chemotherapy

For multiple day cisplatin therapy, to prevent acute nausea and vomiting the use of a 5-HT3- RA and a corticosteroid is recommended on the days when cisplatin is administered to the patients. In addition, for prevention of delayed emesis, a corticosteroid alone should be given. Aprepitant may be useful for multi-day chemotherapy regimens that are likely to be highly emetogenic. Use of 5-HT3- RA on day 1-5 or Palonosetron on days 1, 3, 5 is also recommended.

5.   Therapy in High Dose Chemotherapy

When high dose chemotherapy is to be administered, 5HT3-RA and corticosteroids should be given to the patients before initiating chemotherapy. For prevention of delayed nausea and vomiting after this high dose chemotherapy only corticosteroids on day 2-3 is recommended by the guidelines. Palonosetron or NK-1 RA can also be added in this regimen, however it is not recommended by the recent guidelines.

6.   Treatment of breakthrough CINV

According to NCCN guidelines the general principle of treatment for breakthrough CINV is to add one drug from a different class than in the patient's current regimen. Any of the following drug can be selected: Olanzapine, lorazepam, cannabinoid (e.g. dronabinol, nabilone), haloperidol, metoclopramide, transdermal scopolamine, phenothiazine (e.g. promethazine, prochlorperazine), 5-HT3 RA or dexamethasone.

Recent advances in CINV

Dronabinol and Nabilone are both synthetic tetrahydrocannabinol (THC) which are approved by FDA for treatment of CINV after the failure of a trial of first-line anti-emetics. Exact mechanism of

action of cannabinoids is still unknown but it is thought to act on centrally located CB1 receptors and 5-HT3 receptors in the dorsal vagal complex (DVC), which mediates emesis.[8]

In April 2018 NEPA (Netupitant/palonosetron) the first new antiemetic combination of the highly selective NK-1 RA, netupitant, and the 5-HT3 RA, palonosetron was granted FDA approval.[2,9]

Conclusion

There are many advances in the treatment of cancer like different targeted therapies and immunotherapies, which may complement rather than replace chemotherapy. Hence, chemotherapy remains the mainstay in the treatment of cancer. CINV is the most common side effect associated with chemotherapy which can worsen the quality of life of cancer patients. But with the better understanding of the pathophysiology of CINV and with the research of newer drugs like 5HT3- RA, NK-1 RA, the management of CINV has improved significantly in the last decade. However, such research should continue in the future also to explore newer combinations and newer drugs to decrease the incidence of CINV.

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DRUG INDUCED PIGMENTARY DISORDERS

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Introduction

Skin is considered as the largest organ of the body and is vital for protecting the internal environment from the external environment. Skin consists of three main parts: the epidermis, dermis and the hypodermis. The epidermis is composed of stratified squamous epithelium which is further divided into five different layers.[1]

Various types of cells such as langerhans cells, melanocytes and keratinocytes are found in the epidermis. Keratinocytes constitute the major bulk of the epidermis. Embryologically, they first appear in the basal layer of the epidermis. As cell division and differentiation progress, majority of keratinocytes move upwards forming the different layers of the epidermis while, a minority of them remain in the basal layer as stem cells.[1]

In contrast to keratinocytes, melanocytes are derived from the neural crest cells. They later migrate into the basal layer of the epidermis, where they produce melanosomes. Melanosomes are organelles that convert tyrosine to melanin, giving, skin its colour. These organelles are subsequently transferred into keratinocytes.[2] The concentration of melanocytes is equal in all races. However, it is the size of melanosomes that impart the characteristic skin colour. Larger the melanosomes, darker is the colour. Hypopigmentation or lightening of skin results when melanocytes decrease in number or are unable to produce or transport enough melanin despite adequate numbers.[3] On the other hand, there are situations that can lead to darkening or hyperpigmentation of skin. These include increased production of melanosomes in response to certain hormones or irritation and hyperplasia of melanocytes resulting from exposure to sun or idiopathic causes.[2]

Abnormal pigmentation of skin is a less morbid condition in itself but can prove to be a major cause of psychological and emotional distress in people. This could in turn contribute to a poor quality of life.[4]

Etiology of pigmentary disorders

Pigmentary disorders not only affect skin but can also affect other structures such as hair, nails, cornea, mucosa and some internal organs. Hypopigmentation or loss of pigment is commonly seen in conditions such as vitiligo, pityriasis alba and tinea versicolor. On the other hand, common etiologies of hyperpigmentation include, melasma, solar lentigines, ephelides, and café au lait macules. Besides these, post-inflammatory hypo- and hyper- pigmentation also are commonly reported.[3]

Drugs have also been implicated in causing pigmentary disorders. Drugs such as topical corticosteroids and topical retinoic acid etc. can cause hypopigmentation. Several drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), phenytoin, anti-malarials, amiodarone etc. are known to cause hyperpigmentation. Some drugs may cause fixed drug eruptions, which are followed by localized hyperpigmentation and gradual fading. Fixed drug eruptions which present as plaques with post inflammatory hyperpigmentation have been associated with drugs such as barbiturates, ibuprofen and sulfonamides. PUVA (Psoralen and ultraviolet-A light) therapy may also cause ephelide-like (freckles) pigmentation in some patients.[5]

Changes related to hair following intake of systemic medications occur mostly in the form of hair loss or hypertrichosis. However, change in hair colour is an uncommon adverse effect. Hair of the scalp and/or body hair may involve lightening/greying, darkening, or even a complete change of colour. These side effects have been recently reported more frequently due to increasing use of new target therapies.The underlying mechanisms of hair changes however, remain often unknown.[6]

A.   Drug-induced hypopigmentation

Mechanisms of drug-induced hypopigmentation

Melanocytes respond to cutaneous inflammation and trauma with normal, increased or decreased melanin production. This characteristic is genetically pre-determined and inherited in an autosomal dominant pattern.Thus, people who are genetically prone to have melanocytes with high susceptibility to damage, are more likely to develop hypopigmentation. On the other hand, those with lower susceptibility to damage may tend to develop hyperpigmentation. It is suggested that hypopigmentation may result from inhibition of melanogenesis rather than destruction of melanocytes however, severe inflammation may lead to loss of melanocytes or even melanocyte death thus causing permanent pigmentary changes.[7]

Drugs causing hypopigmentation

Drug-induced hypopigmentation is most commonly associated with topical agents. The phenomenon normally appears 2-6 months after treatment has been started. Drugs such as hydroquinone, azelaic acid, kojic acid, topical retinoids, topical and intra-lesional corticosteroids and glycolic acid affect melanogenesis, further causing hypopigmentation. However, this feature is put to advantage for treatment of skin conditions such as melasma.[8] Latanoprost also has been reported to cause skin hypopigmentation.[9] Chloroquine and cancer chemotherapeutic agents can also cause depigmentation of hair.[10] Hypopigmentation also includes vitiligo, which can cause a greater concern than other reversible forms of hypopigmentation. Vitiligo leads to much emotional stress and affects a person's quality of life, hence mandates early treatment.[11]

Vitiligo may be drug-induced or non-drug-induced. In either case, the clinical presentation is the same with the exception that drug-induced vitiligo is characterized by a rapid onset and progression. The mechanism of how a drug induces vitiligo remains unclear but certain autoimmune, neural and cytotoxic theories are being considered as underlying mechanisms. Drug-induced vitiligo appear mostly on face, elbows and knees, the backs of hands, and the genitals. These are patches of depigmented areas with irregular but well-defined borders.[5]

Drugs causing vitiligo usually are immune-modulating, biologics or targeted medicines.These include topical imiquimod, interleukins [IL-2, IL-4], and interferon, tumour necrosis factor inhibitors such as infliximab, adalimumab, and etanercept, programmed death receptor inhibitors Pembrolizumab and Nivolumab, BRAF inhibitors Vemurafenib and Dabrafenib, tyrosine kinase inhibitors Imatinib and Gefitinib. Rarely, anticonvulsants, Levodopa, antimalarials such as Hydroxychloroquine have also been implicated. Certain phenols such as monobenzyl ether of Hydroquinone which cause localized hypopigmentation known as leukoderma, rarely may cause generalized vitiligo as well.[12]

Management of drug-induced skin hypopigmentation

Management requires discontinuation of the offending drug. Rate of recovery however differs from patient to patient. In the meantime, cosmetics may be used as camouflage. Sunscreens, phototherapy, topical corticosteroids and calcineurin inhibitors may be additionally helpful. Psoralen and Ultraviolet A (PUVA) therapy, excimer laser therapy and skin grafts taken from normally pigmented areas may help improve cosmesis in later stages.[13,14,15]

B.   Drug-induced hyperpigmentation

Mechanisms of drug-induced hyperpigmentation

Several mechanisms are involved in the drug-induced hyperpigmentation of the skin. In case of heavy metals such as iron, silver and gold, damage to dermal vessels leads to their deposition in the dermis. When deposited in sufficient quantities, a distinctive change in skin colour is seen without any significant increase in melanin.[16]

Some drugs such as phenothiazines on prolonged use, react with melanin to form a drug-pigment complex. Such complexes are difficult to metabolize and hence accumulate in the layers of the skin.[17] Exposure to sunlight may further aggravate the process. Drugs may also be transformed into visible particles after being taken up by dermal macrophages under the influence of sunlight. Other drugs may induce hypermelanosis as a non-specific post-inflammatory change in predisposed individuals which may be worsened by exposure to sun. Some drugs induce pigmentation directly by accumulating and/or reacting with other substances in the skin.[18] For example, pigmentation by phenytoin is induced by its direct action on melanocytes causing dispersion of melanin granules in the epidermis.[17]

Drugs causing hyperpigmentation

It is known that drug induced skin hyperpigmentation accounts for 10-20% of all cases of acquired hyperpigmentation.[5,17]

Sr. No.	Drugs	Structures involved	Characteristic feature	Reversibility
1.	Heavy metals			
a.	Iron	Skin	Dark brown pigmentation (Siderosis)	Irreversible
b.	Gold	Sun-exposed areas of skin	Diffuse bluish-grey pigmentation in (Chrysiasis)	Irreversible
c.	Silver salts	Skin, nails, sclera	Diffuse greyish pigmentation (Argyria)	Irreversible
2.	Tetracyclines (minocycline)	Skin, teeth and nails	Bluish pigmentation especially in scars	Reversible
3.	Antipsychotics	Skin, conjunctiva, cataracts, corneal opacities, nails	Bluish-grey pigmentation, especially in sun-exposed areas	Irreversible
4.	Tricyclic antidepressants: (Imipramine)	Skin, hair and nails	Slate-grey pigmentation	Reversible
5.	Anticonvulsants: (Phenytoin)	Skin	roughly symmetrical dark brown patches on face resembling chloasma	Reversible
6.	Antimalarials (chloroquine or hydroxychloroquine)	Skin, mucosa (especially hard palate), nail beds, cornea, retina	Bluish-black patches, especially in sun-exposed areas	Reversible
7.	Cytotoxic drugs (Busulfan, Cyclophosphamide, Bleomycin and Adriamycin)	Skin, hair, nails	Brownish pigmentation	Reversible
8.	Antiarrhythmic: Amiodarone	Skin	Blue-grey pigmentation	Reversible
9.	NSAIDs	Skin of face, extremities and genitalia	Associated with fixed drug eruptions	Reversible
10.	Clofazimine	Skin and nails	Generalized brown pigmentation	Reversible
11.	Zidovudine	Tongue, buccal mucosa and palate, Nails	Brown pigmentation	Reversible

Inadvertent subcutaneous administration of iron may lead to siderosis at the site of injection. Gold, which was previously used for treatment of rheumatoid diseases and silver used in food products such as sweets are known to cause pigmentation of skin which are usually permanent in nature.[5]

Among all tetracyclines, minocycline tends to have the highest potential for pigmentation of skin and oral mucosa, in addition to other organs. Other drugs such as hydroquinone, methyldopa, disulfiram, imatinib, oral contraceptives and hormone replacement therapy have also been reported to cause hyperpigmentation.[5]

Management of drug-induced skin hyperpigmentation

Drug-induced skin pigmentation is a cosmetically disfiguring condition especially if it occurs on exposed areas. In most cases, lesions resolve once the offending drug has been stopped.For example, chloroquine and methyldopa.However, the pigmentation may last a long time or become permanent. Resolution of lesions caused by drugs such as minocycline and imipramine take several years after the drug is stopped. Drugs that induce skin pigmentation also tend to cause photosensitivity reactions hence, sun protection is usually recommended.Laser treatment has also been found to be successful as an option for treating certain drug-induced skin pigmentation .[5,17]

Conclusion

Drug-induced pigmentary changes can be managed by identifying and discontinuing the offending drug. Most mucocutaneous pigmentation are reversible and spontaneously resolve when the inciting drug is withdrawn. In situations where several drugs may be implicated, it is prudent to decide, on a case to case basis, to stop all nonessential medications. If a drug is considered essential, decreasing the dose of the drug is often sufficient to diminish drug-related dyspigmentation.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(November 2018 to February 2019)

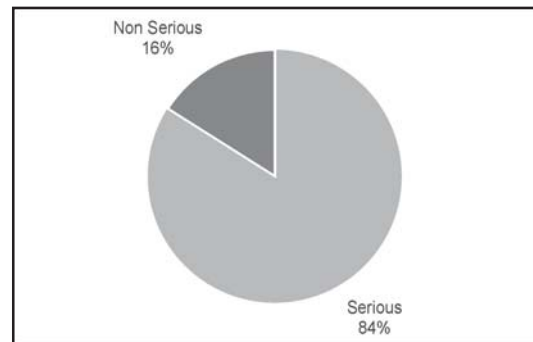**Compiled by Dr. Monika Bhanushali*, Dr. Harshad Katyarmal*, Dr. Neha Shende***

* - 2nd year residents, Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Total no. of cases: N = 136

1.   **Age and Gender distribution**

Age group (years)	No. of patients	Males	Females
<3	5	3	2
3 to 17	27	16	11
18-44	47	16	31
45-60	32	21	11
>60	25	8	17
Total	136	64	72

2.   **Seriousness of the ADR: N=136**

3.   **System involved in ADR: N=136**
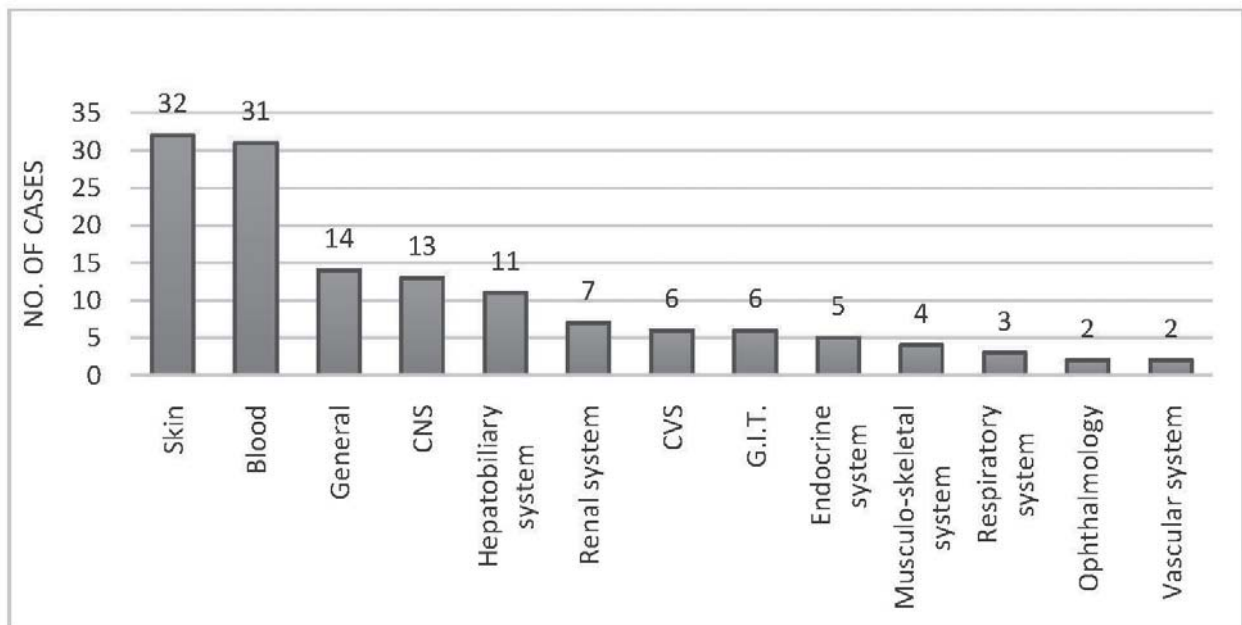
4.   Class of the suspected drug: N=176

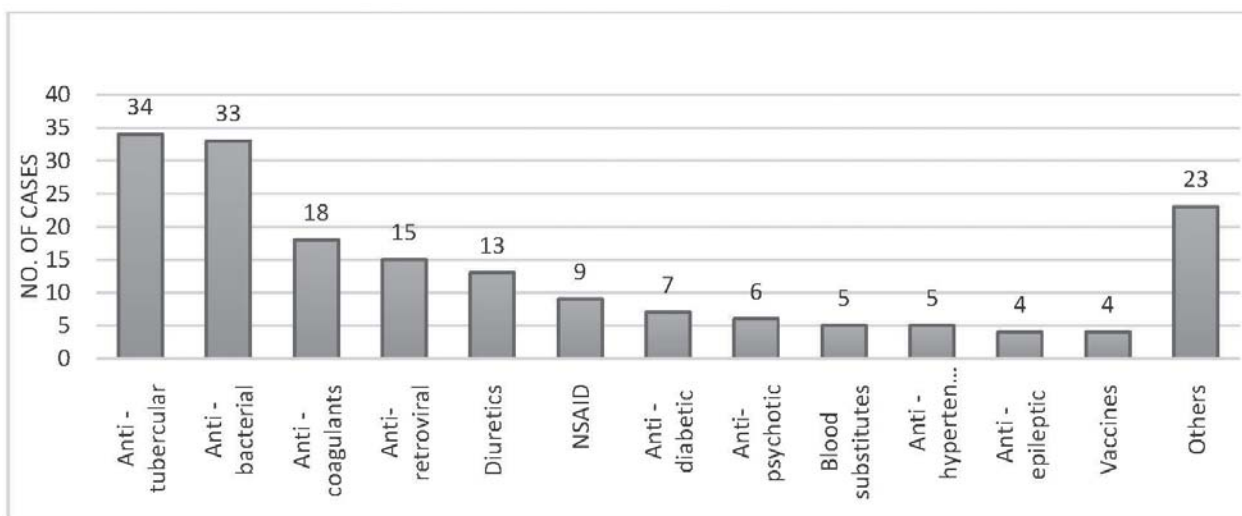*Other* class of drugs include Anti-Arrhythmic, Anti-asthma, Nutritional supplements, Anti-Glaucoma, Anti-Cancer, Anticholinergic, Anti-emetic, Anti-Fungal, Anti-spasmodic, Aquaretic, Benzodiazepine, Chelating agent, Cholinesterase inhibitors, Contrast, Immunoglobulins, Proton Pump Inhibitor.

5.   Outcome of the reaction: N=136
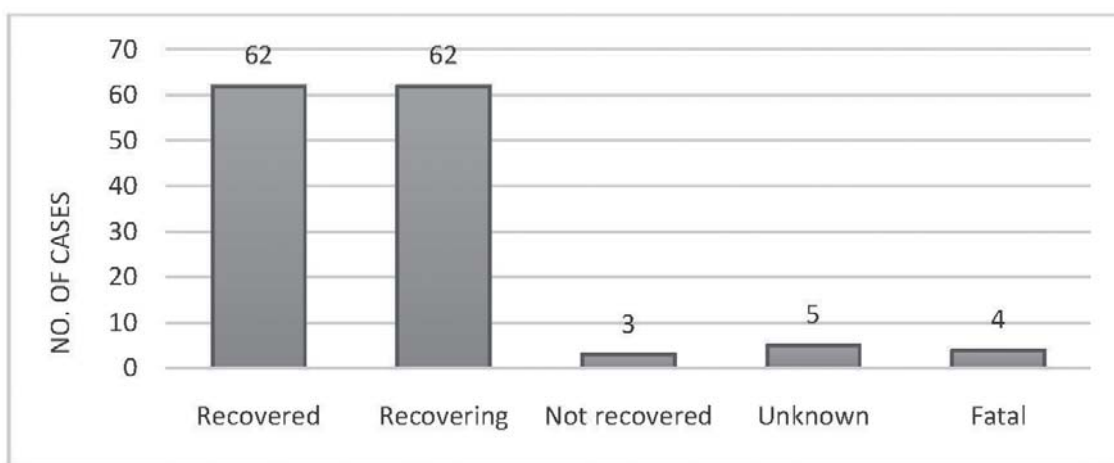
6.   Causality assessment (WHO UMC Classification) : N=136
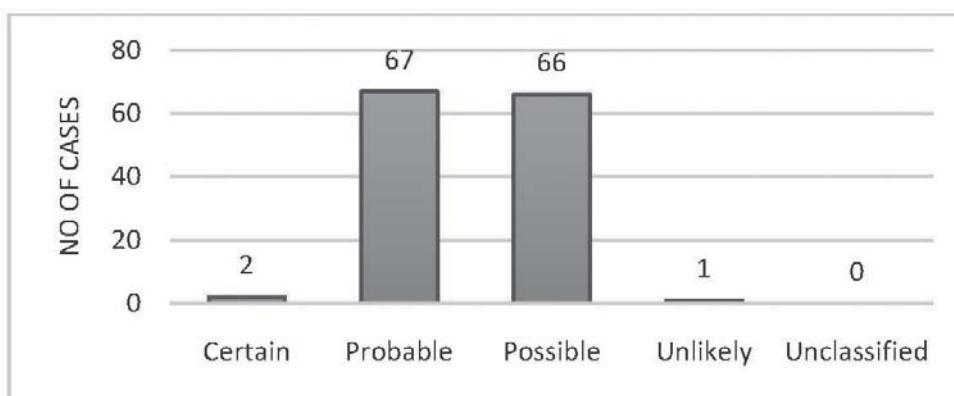
EVALUATION OF A CASE
Metformin induced lactic acidosis
Dr. Monika Bhanushali* and Dr Iravati Waghmare**

*-2nd Year Resident, Department of Pharmacology; ** - 3rd Year Resident, Department of Medicine, LTMMC & GH, Sion, Mumbai

Introduction:

Biguanides, a class of oral antihyperglycemic agents used in type 2 diabetes mellitus, include phenformin, buformin and metformin. Use of phenformin and buformin is discontinued in the world since 1970s because of unacceptable rates of associated lactic acidosis.[1] This great concern about lactic acidosis delayed the US market introduction of metformin until May 1995.[2] The results of the United Kingdom Prospective Diabetes Study (UKPDS) have provided good evidence of the benefits of metformin on the long-term incidence of diabetic complications in overweight patients.[3] More recently it has also been used to improve fertility and weight reduction in patients with polycystic ovary syndrome.[4]

Lactic acidosis is the most frequent cause of metabolic acidosis and is characterized with increase in anion gap.[2] Various drugs can cause lactic acidosis. They include metformin, linezolid, propofol, isoniazid and nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) such as didanosine, stavudine, lamivudine, zidovudine, abacavir.[5] Metformin induced lactic acidosis is a rare complication, but it is potentially life threatening, and its incidence is estimated to be 3.3 cases per 100,000 person-years.[6]

Here we discuss a case of metformin induced lactic acidosis reported at a tertiary care hospital in Maharashtra.

Case report:

A 30-year-old female patient was diagnosed with gestational diabetes mellitus in her first trimester (April 2018) and was started with metformin 500 mg twice a day. The dose of metformin was titrated to 500 mg thrice a day in her third trimester (September 2018) due to inadequate blood sugar levels control. The patient was advised to continue the treatment with metformin post-delivery as her sugar levels did not normalise.

The patient presented to the hospital a month after her delivery with complaints of fever, chills and breathlessness which later worsened, and the patient became unconscious and was admitted to the medical intensive care unit for further management.

The patient had history of manic-depressive disorder and was on the treatment with tablet escitalopram 5 mg and mirtazapine 150 mg since last 3 years (January 2016). There was no history of diarrhoea,

pain in abdomen, toxic ingestions, infectious symptoms and recent medication changes. Patient also denied any history of substance abuse. There was no history of a recent major surgery, renal dysfunction or liver disease.

On laboratory investigations, her complete blood counts, serum electrolytes, liver and kidney function parameters were within normal range. Her serum glucose levels were also within normal range. The pH of the blood was 7.101 (normal range 7.35-7.45), serum bicarbonate levels were 9 mEq/L (normal range 23-30 mEq/L) and serum lactate levels were 148.4 mg/dL (normal range 4.5-19.8 mg/dL). Hence a diagnosis of lactic acidosis was made.

Metformin was suspected for the lactic acidosis as all the other causes were ruled out. Metformin was stopped on the same day. i.e. day of admission. Other medications i.e. escitalopram and mirtazapine were continued. The medications were not found to have any drug-drug interactions.[7]

Two days following withdrawal of metformin, the pH had raised to 7.138, serum bicarbonate levels had increased to 11 mEq/L and serum lactate had reduced to 115 mg/dL. As these levels showed improvement after withdrawal of metformin, a diagnosis of metformin induced lactic acidosis was confirmed.

This adverse drug reaction (ADR) was considered "serious" as per seriousness criteria as it was "life threatening". The severity of the ADR was "moderate" as the ADR was the reason for the patient's hospitalization as per 'modified Hartwig Siegel scale'.[8] There was temporal association between the drug intake and the occurrence of the ADR. There were no other concurrent diseases or concomitant medications which could have precipitated the presented ADR. Also, the patient recovered after withdrawal of the drug, hence de-challenge of the drug was positive. Based on these criteria as per WHO UMC causality assessment scale, the causal association of the lactic acidosis with metformin was deemed "PROBABLE".

Discussion:

Lactic acid is an endogenous acid and lactic acidosis is the most frequent cause of metabolic acidosis.[2] The standard working definition of lactic acidosis is an arterial lactate concentration exceeding 5 mmol/L or serum lactate > 45 mg/dL and pH <7.35 which is also known as the 'Luft criteria'.[9,10]. The types of lactic acidosis can further be broken down into types A and B. In general, type A can be attributed to tissue hypoxia or global hypoperfusion, as seen in circulatory collapse or in the setting of increased anaerobic activity.[11] Type B lactic acidosis occurs in the absence of tissue hypoperfusion and comprises a heterogeneous group of aetiologies, including intoxications, liver failure, malignancy, rare hereditary enzyme deficiencies, and certain medications, as seen in our patient.[12] Thus, in our case the lactic acidosis due to metformin is primarily of type B.

Metformin likely inhibits gluconeogenesis by blocking pyruvate carboxylase, the first step of gluconeogenesis, which converts pyruvate to oxaloacetate. Blocking this enzyme leads to accumulation of lactic acid.[13] Metformin inhibits mitochondrial cellular respiration in tissues (i.e., liver and muscle) responsible for lactate removal, which increases anaerobic metabolism.[11] Metformin also inhibits complex I of the mitochondrial electron transport chain (ETC) which increases NADH/NAD+ ratio. This blocks the entry of pyruvate into the tricarboxylic acid cycle, hence it undergoes anaerobic metabolism and lactic acid is generated. Metformin also decreases hepatic metabolism of lactate and has a negative ionotropic effect on the heart, both of which can elevate lactate levels.[13] This results in both accelerated lactate production and reduced lactate metabolism.[14]

The most important risk factor for lactic acidosis due to metformin is acute renal insufficiency with progressive derangement in kidney function. In patients with deranged renal function, metformin accumulation occurs as metformin is excreted from the proximal tubules of kidney without being metabolised. Other risk factors also include volume depletion, low cardiac output, anaemia, compromised liver function, hypoxaemia or acute infection.[15] Lactic acidosis occurring in patients receiving metformin with these predisposing factors is labelled as Metformin associated lactic acidosis (MALA). However, if lactic acidosis cannot be explained by any major risk factor other than metformin, then it is called as metformin induced lactic acidosis.[16] As the above-mentioned risk factors were absent in our case, it can therefore be termed as metformin induced lactic acidosis.

The treatment of metformin induced lactic acidosis consists of supportive care, elimination of the offending medication with renal function replacement therapies (i.e. haemodialysis and continuous hemofiltration).[2] The supportive care includes mechanical respiratory support for patient with respiratory distress, haemodynamic instability or depressed sensorium; assurance of adequate systemic perfusion, correction of fluid deficits or electrolyte abnormalities with intravenous fluid.[17] The metabolic acidaemia should be neutralised with NaHCO3. The renal function replacement therapy (i.e. haemodialysis and continuous hemofiltration) is recommended with keeping a view to restore the blood volume, enhance the renal blood flow, correction of the metabolic acidosis and removal of lactate and metformin.[2]

Conclusion:

This case demonstrates that although lactic acidosis due to metformin is a rare adverse event, it is life threatening and can occur in the absence of any risk factors. It should be suspected in patients receiving metformin and presenting with symptoms of lactic acidosis.

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PUBLISHED LITERATURE ON METFORMIN INDUCED LACTIC ACIDOSIS

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Metformin-induced lactic acidosis: a case series

Silvestre J, Carvalho S, Mendes V, Coelho L, Tapadinhas C, Ferreira P, et al

J Med Case Rep. 2007;1:126

Case presentation: We present two case reports of metformin-associated lactic acidosis. The first case is a 77 years old female with a past medical history of HT and type 2 DM who had recently been prescribed metformin (3 g/day), perindopril and acetylsalicylic acid. She was admitted to emergency department two weeks later with abdominal pain and psychomotor agitation. Physical examination revealed only signs of poor perfusion. Laboratory evaluation revealed hyperkalemia, elevated creatinine and blood urea nitrogen and mild leukocytosis. Arterial blood gases showed severe lactic acidemia. She was admitted to ICU. Vasopressor and ventilatory support was initiated and continuous venovenous hemodiafiltration was instituted. 24 hours later, full clinical recovery was observed, with return to a normal serum lactate level. The patient was discharged from the ICU on the 6th day. The 2nd patient is a 69 year old male with a past medical history of HT, type 2 DM and IHD who was on metformin (4 g/day), gliclazide, acetylsalicylic acid and isosorbide dinitrate. He was admitted to the emergency department in shock with extreme bradycardia. Initial evaluation revealed severe lactic acidosis and elevated creatinine and urea. The patient was admitted to the ICU and commenced on continuous venovenous hemodiafiltration in addition to other supportive measures. A progressive recovery was observed and he was discharged from the intensive care unit on the 7th day.

Conclusion: We present two case reports of severe lactic acidosis most probably associated with high doses of metformin in patients with no known contraindications for metformin prescription. In both patients no other condition was identified to cause such severe lactic acidosis.

Metformin-Associated Lactic Acidosis: A Case Report

Umeda T, Minami T, Bartolomei K, Summerhill E.

Drug Saf Case Rep. 2018 Feb 9;5(1):8.

A 54-year-old woman with type 2 diabetes mellitus, hypertension, and peripheral vascular disease developed life-threatening lactic acidosis during treatment with metformin for type 2 diabetes. The woman received metformin at 1000 mg orally twice a day for type 2 diabetes. She presented to our emergency department with a 3-day history of severe watery diarrhea, nausea, and vomiting. Her

grandson whom she cared for had gastroenteritis several days prior to the onset of her symptoms. She was confused and hypotensive with a blood pressure of 70/39 mmHg. Her initial laboratory findings were remarkable with an arterial blood gas pH 6.57, HCO3 - 2 mEq/L, anion gap 30 mmol/L, and lactate 16.3 mmol/L. She was diagnosed with severe lactic acidosis. Metformin was discontinued. Upon arrival in the emergency department, she became unresponsive and experienced a pulseless electrical activity cardiac arrest. After resuscitation, her severe acidemia persisted despite aggressive intervention with volume resuscitation and vasopressors, leading to the initiation of renal replacement therapy. After multiple dialysis treatments, her severe acidemia resolved. Serum metformin concentration from presentation ultimately returned to 42 mcg/mL (therapeutic concentration: 1-2 mcg/mL). She was discharged from the hospital on day 15 without any neurologic complications. A Naranjo assessment score of 8 was obtained, indicating a probable relationship between the patient's lactic acidosis and her use of the suspect drug.

Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment.

Bruijstens LA, van Luin M, Buscher-Jungerhans PM, Bosch FH.

Neth J Med. 2008 May;66(5):185-90.

Background: Lactic acidosis in metformin use is a widely recognised but rare side effect. Case reports usually describe elderly patients with conditions which in themselves can cause lactic acidosis or with known contraindications to metformin. We present cases of an elderly woman, a younger woman and a man who developed serious metformin-induced lactic acidosis in the absence of chronic renal impairment.

Results: Laboratory results showed acute renal failure in all patients. The pH was 6.77, 6.98 and 6.7, respectively, and lactate levels were 18.2, 18.4 and 11.7 mmol/l, respectively. Metformin plasma levels were 58, 57 and 39 mg/l. All patients received continuous veno-venous haemofiltration (CVVH), using bicarbonate as a buffer solution shortly after arrival on our ICU. In the subsequent hours, a steep decline in the plasma levels was observed, with a concomitant increase in pH. No other diagnoses were made, so we concluded that all patients were suffering from metformin-induced lactic acidosis. Despite the severity of the metabolic acidosis, both female patients survived. Our male patient died after a prolonged stay in the ICU, but this was not related to metformin.

Conclusion: Metformin-induced lactic acidosis does exist. Metformin-induced lactic acidosis may occur in patients with previously normal renal function, even in young patients. Patients with extreme (lactic) metabolic acidosis caused by metformin can survive when CVVH treatment is initiated rapidly. Intercurrent symptoms or diseases that affect renal perfusion can precipitate lactic acidosis.

REGULATORY UDATE AND MEDICAL NEWS

Compiled by Dr Roshni Panchal* and Dr. Shankhini Deshpande**

* - Specialty Medical Officer; ** - 1st Year Resident, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Lamotrigine: Drug Safety Communication- serious immune system reaction

Background: Lamotrigine is used alone or with other medicines to treat seizures and for treatment in patients with bipolar disorder. Lamotrigine has been approved and on the market for 24 years.

Issue: FDA is warning that the medicine lamotrigine for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's immune system. The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, and multiorgan damage. The condition can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. Hence, warning about this risk be added to the prescribing information in the lamotrigine.

Recommendation: Health care professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). It is recommended to evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:

- Fever and rash
- Enlarged spleen
- Cytopenias
- Elevated levels of triglycerides or low blood levels of fibrinogen
- High levels of blood ferritin
- Hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
- Decreased or absent Natural Killer (NK) Cell activity
- Elevated blood levels of CD25 showing prolonged immune cell activation

Reference: Epvc.gov.eg. 2019 [cited 2 April 2019]. Available from: http://epvc.gov.eg/media/pvnewsletters/107_Newsletter-Hundred_and_Seven_December_2018.pdf

Atorvastatin: Drug Safety Communication- Co-administration with antivirals- increases atorvastatin levels.

Background: Atorvastatin is a synthetic lipid lowering agent indicated for the prevention of cardiovascular diseases and hypercholesterolaemia. Based on the review of the data on safety and efficacy, the benefit-risk balance of atorvastatin-containing medicinal products in the approved indication(s) remains unchanged. Nevertheless, the information is updated regarding its use with antivirals such as Elbasvir/grazoprevir and glecaprevir/pibrentasvir preparations which are indicated for the treatment of hepatitis C (HCV).

Issue: The Egyptian Pharmaceutical Vigilance Center (EPVC) has announced an update to include a warning about the potential increase in atorvastatin levels when co-administered with antiviral drugs such as elbasvir/grazoprevir and glecaprevir/pibrentasvir.

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products which are potent inhibitors of CYP3A4 or transport proteins that may increase its own plasma concentration. Risk of myopathy may be increased with the concomitant use of atorvastatin and antivirals for treatment of HCV.

Reference: WHO Pharmaceuticals Newsletter.2019 [cited 2019 April 2].(1) Available from: https://apps.who.int/iris/bitstream/handle/10665/311036/WPN-2019-01-eng.pdf?ua=1

Infliximab: Drug Safety Communication- causing mycosis fungoides

Background: Infliximab is a monoclonal antibody indicated for autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

Issue: The Therapeutic Goods Administration (TGA) has updated information regarding infliximab causing mycosis fungoides. The TGA identified a safety signal based on three local reports of adverse events related to infliximab. The number of observed reports of mycosis fungoides with the use of infliximab is higher than expected. After detailed analysis of the signal, the TGA is working to add information about mycosis fungoides to the adverse effects section of the drug.

Reference: WHO Pharmaceuticals Newsletter.2019 [cited 2019 April 2].(1) Available from: https://apps.who.int/iris/bitstream/handle/10665/311036/WPN-2019-01-eng.pdf?ua=1

MATCH THE FOLLOWING DRUG WITH ITS SPECIFIC ADR

Dr SharmadaNerlekar*, Dr AbhilashaRashmi*

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1	Quetiapine		A	Immunoglobulin light chain proteinuria
2	Fomivirsen		B	Haemolytic anaemia
3	Ketoprofen		C	Breast tenderness
4	Oxaliplatin		D	Acneiform rash
5	Aprepitant		E	Rise in serum triglycerides
6	Didanosine		F	Nephrolithiasis
7	Paclitaxel		G	Blistering on extravasation
8	Filgrastim		H	Pancreatitis
9	Rifampicin		I	Iritis
10	Leuprolide		J	Fluid retention in elderly
11	Indinavir		K	Pericardial effusion
12	Colestipol		L	Neutropenia
13	Epirubicin		M	Pharyngo-Laryngeal Dysaesthesia
14	Gefitinib		N	Rise in serum prolactin
15	Methyldopa		O	Deep vein thrombosis

Answers : 1- N; 2- I; 3- J; 4- M; 5- O; 6- H; 7- L; 8- K; 9- A; 10- C; 11- F; 12- E; 13- G; 14- D; 15- B.

ALPHABET 'U' PUZZLE

Dr. Abhilasha Rashmi*, Dr. Sharmada Nerlekar*

*Associate Professor, Department of Pharmacology,
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1 U									
2	U								
3		U							
4			U						
5				U					
6					U				
7						U			
8							U		
9								U	
10									U

1. Headache and abdominal pain are the most severe adverse effects seen with this 19-norprogesterone derivative which acts for about 120 hours as an emergency contraceptive.

2. The most commonly noted adverse events with this antifungal agent used against resistant microsporidia infection are leukopenia & thrombocytopenia.

3. The incidence of withdrawal symptoms with discontinuation is less with this SSRI, as compared to other SSRIs, because its active metabolite has a long half life of about 1-2 weeks.

4. The combination of this NK1 receptor antagonist along with Palonosetron, is FDA approved in 2016 for chemotherapy induced nausea & vomiting.

5. Total doses greater than 900mg/m2 of this Anthracycline, used for the treatment of breast cancer, sharply increases the risk of cardiotoxicity.

6. Patients may develop decrease in reticulocyte & neutrophil count and increase in transaminase levels by Artemisinin derivatives such as _____.

7. Being a substrate of the efflux transporters Pgp& BCRP, this anti hepatitis C virus drug should not be used with potent inducers of these transporters like Rifampicin, Phenytoin, Carbamazepine etc.

8. This heme-independent activator of soluble guanylyl cyclase, proposed for the treatment of acute heart failure, is found to increase the rate of symptomatic hypotension.

9. Bronchospasm and hypotension are less likely with amino steroid neuromuscular blockers like _____ because they have less tendency to release histamine after intradermal or systemic administration.

10. Since recrudescence is a problem with _____ derivatives for treatment of malaria, these compounds are generally given in combination with other long acting antimalarial agents.

ALPHABET 'U' PUZZLE: ANSWERS :

1. ULIPRISTAL
2. FUMAGILLIN
3. FLUOXETINE
4. NETUPITANT
5. EPIRUBICIN
6. ARTESUNATE
7. SOFOSBUVIR
8. CINACIGUAT
9. VE/ ROCURONIUM
10. QUINGHOUSU

We would like to request all the clinical departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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