

The National Pharmacovigilance Centre Newsletter



MINISTRY OF HEALTH & QUALITY OF LIFE

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EDITORIAL NOTE

Dear Health Professional,

Regardless of what drug we are talking about, Pharmacovigilance is about putting patient's safety first in the use of drugs. We do this by assessing the risk and benefit ratio of the drug. The higher the ratio, the safer the drug.

In this Newsletter, we have chosen to tell you about Nicolau's syndrome, an uncommon but avoidable complication of intramuscular injections leading to variable degrees of necrosis of the skin and variable tissues.

We have also drawn your attention the potential association of the presence of allele HLA B 5801 with severe cutaneous reactions observed with Allopurinol.

The National Pharmacovigilance Centre has been very active during the year 2018. We have:

1. Run several CNEs for the nursing staff in the Regional Hospitals,
2. Organised training sessions for the Pharmacovigilance staff of Wholesale Pharmacies of the private sector
3. Done one CPD for pharmacists and
4. Last and not least, we have launched our newsletter.

All the above, would not have been possible without the collaboration and commitment of the Pharmacovigilance team.

I hope that the good work will continue.

Yours sincerely,

Dr. Yee Kin Tet Hoy Youn

LIST OF ABBREVIATIONS

ADRs – Adverse Drug Reactions

ANSM – Agence Nationale de Sécurité du Médicament

EMA – European Medicines Agency

FDA or USFDA – Food and Drug Administration

HCP – Health Care Professionals

HSA – Health Sciences Authority (Singapore)

NSAID – Non-Steroidal Anti-inflammatory Drug

SCARs – Severe Cutaneous Adverse Reactions

SJS – Stevens Johnson Syndrome

UMC – Uppsala Monitoring Centre

WHO – World Health Organisation

Allopurinol and severe cutaneous adverse reactions

Dr. Yee Kin Tet Hoy Youn, Chairperson, The National Pharmacovigilance Committee

Allopurinol can cause severe cutaneous adverse reactions like Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic syndromes (DRESS).

The risk of SJS/TEN/DRESS is associated with the HLA B 5801 allele

The frequency of the HLA B 5801 allele varies across different ethnic population:

- Han Chinese: up to 20%
- Thai: 8-15%
- Korean: 12%
- African/Indian: up to 7%
- European/Japanese :1 -2 %

The European medicine agency (EMA) and the American college of Rheumatology (ACR) recommend that screening for HLA B 5801 should be considered before starting allopurinol in sub group patient where prevalence is high.

In Mauritius several cases of SJS/TEN have been reported.

Medical practitioners in Mauritius are advised to exercise caution in prescribing allopurinol and to inform the patient to stop the medication immediately in case of skin rash.

Nicolau Syndrome – a severe ADR with the use of injectables

Mrs. S. Boolell, Mr. V. Mooneeramsing; The National Pharmacovigilance Centre, Mauritius

Introduction

Typical drug reaction can be either systemic or localised. Pain at the injection site, abscess formation or nerve damage are possible. Allergic reactions to the medication may be minor to life-threatening. However, extensive tissue necrosis is rare. One such tissue reaction is called Nicolau syndrome (NS). This syndrome is also called embolia cutis medicamentosa or livedo-like dermatitis. This syndrome was first described by Freudenthal in 1924 and Nicolau in 1925 in patients receiving IM bismuth for syphilis

treatment^[1,2]. NS has occurred with almost all classes of medications, including Non-Steroidal Anti-Inflammatory drugs (NSAIDs), antipsychotics, local anaesthetics, corticosteroids, antibiotics, Vitamin B, antihistamines and vaccines^[3]. Several cases of NS has been reported with Diclofenac, a Non-Steroidal Anti-Inflammatory drug. Case studies have indicated that this may occur in various anatomical locations and following either IM, IA, IV or SC injections^[3,4].

Pathogenesis and etiology

Pathogenesis of NS is not clear but a vascular origin is the most reasonable hypothesis. Acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole are the key mechanisms^[5]. The leakage of around artery and neural space has been suggested as cause of intense pain. Moreover, sympathetic nerve stimulation

and vasospasm lead to ischemic change and skin necrosis. Unintended intravascular injection of drugs also has been proposed as causing inflammation or thromboembolic occlusion of the arterioles. These may cause arterial intimal necrosis, destructure the arterial membrane and induced subsequently cutaneous necrosis^[6].

Many drugs related to NS have been reported. Examples are as follows:

Table 1

	Target disease or symptom of using drug	Reference	Duration of necrosis	Affected site
Naltrexone	Alcohol dependency	Perli et al [7]	Over 7 days	Buttock
Etanercept	Psoriatic arthritis	Guarneri et al [8]	10 days	Abdomen
Ketorolac	Non-specific	Marangi et al [9]	2 weeks	Buttock
Chlorpheniramine maleate	Pruritus	Nischal et al [10]	7 days	Arm
Salicylate bismuth	sypphilis	Corazza et al [11]	A few days	Buttock, thigh
Benzathine penicillin	Non specific	De Souza et al [12]	1 day	Lower extremity
DPT	Vaccination	Erkek et al [13]	2 weeks	Thigh
DPT-polio- Hib	Vaccination	Bégin et al [14]	2 weeks	Thigh
Vitamin k	Prematurity	Puvabanditsin et al [15]	2 weeks	Thigh

Clinical features and phases of Nicolau Syndrome

Clinical features of various patients suffering from NS are divided into three steps: initial, acute and necrotic phases.

Table 2

Phase	Clinical Features	Treatment
Initial	<ul style="list-style-type: none"> • Bluish discoloration • Intense pain • Erythema • Radiating pain • Faintness, syncope 	<ul style="list-style-type: none"> • No ice pack • Analgesics • Systemic antibiotics
Acute (24 hrs. to 3 days later)	<ul style="list-style-type: none"> • Livedoid plaque • Violaceous patch • Non-necrotic 	<ul style="list-style-type: none"> • Systemic steroid • Anticoagulant agent
Necrotic (5 days to 2 weeks)	<ul style="list-style-type: none"> • Necrotic indurated plaque • Ulceration with necrosis 	<ul style="list-style-type: none"> • Surgical debridement • Plastic surgery

How to prevent Nicolau syndrome

According to Dr. Engin Senel, Clinic of Dermatology, Çankiri, Turkey, several precautions can be taken to avoid Nicolau syndrome.

Healthcare personnel can adopt the following techniques:

- A long (enough to reach muscle) needle should be used. A 90-kg patient requires a 2- or 3-inch (5 – 7.5 cm) needle and a 45-kg patient requires a 1.25- or 1.45-inch needle.
- Injection should be applied in the upper outer quadrant of the buttock.
- Aspirating the needle before injecting the medication should be performed, to ensure that no blood vessel is hit.
- The health care personnel should never inject more than 5 ml of medication at a time when using the Z-track injection method.
- If more than one injection or larger dose is required or ordered, different sites should be chosen.

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Fatal ADR following use of Diclofenac IM

Mr. A. Seeneevassen; Point of Contact – SSRN Hospital

Case presentation

A 60 year old male patient presented himself at the Accident & Emergency Department with high fever. Following diagnosis, he was administered Diclofenac intra-muscularly in the gluteal muscle. After some time, the patient developed severe tissue necrosis at the site of injection. The treating Doctor diagnosed a case of necrotising fasciitis which was fatal.

Diclofenac is a Non-Steroidal Anti-inflammatory Drug (NSAID) that has analgesic, anti-inflammatory and anti-pyretic properties. Its mode of action is by inhibiting cyclo-oxygenase 1 and cyclo-oxygenase 2 enzymes. These enzymes are important in the pathway for the production of inflammatory mediators.

The use of NSAIDs in injectable form is known to have caused tissue necrosis with possible reasons being (1) damage to an end artery and (2) cytotoxic effect of the excipients.

The case was reported to The National Pharmacovigilance Centre for further investigations.

Acetazolamide in ophthalmology **ANSM**

Acetazolamide is a reversible carbonic anhydrase inhibitor. It can be used as a diuretic or for the relief of ocular tension in glaucoma. In the eye, carbonic anhydrase is responsible for the formation of aqueous humour and its inhibition by the drug prevents excessive build-up of aqueous humour.

The most common side effects associated with the use of oral acetazolamide include fatigue, paraesthesia of the face and extremities, metallic taste in the mouth, and nausea and/or vomiting, which are related to drug-induced metabolic acidosis. Other complaints may include dizziness, weight loss, depression, or intestinal colic.

It has been observed that due to risk of teratogenicity and foetotoxicity, the use of acetazolamide is as follows:

- Contraindicated in pregnant women during the first trimester,
- Avoid to prescribe to pregnant women in the 2nd and 3rd trimester, unless there is no other choice.

Women of child-bearing age should be informed about the risks of using acetazolamide and should use any contraceptive during the course of the treatment.

Patients exposed to acetazolamide during their pregnancy should be closely monitored.

Reference: <https://www.anism.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Diamox->

acetazolamide-modifications-importantes-concernant-l-utilisation-chez-la-femme-enceinte-Lettre-aux-professionnels-de-sante

Fluoroquinolone – risk of disabling and potentially long-lasting side-effects **EMA**

EMA's human medicine committee (CHMP) has confirmed that the use of fluoroquinolone antibiotics should be restricted. The prescribing information should describe the disabling and potentially permanent side effects and advise patients to stop treatment with a fluoroquinolone at the first sign of a side effect involving muscles, tendons, joints and the nervous system.

For the following cases, quinolones are to be used if other antimicrobials are not appropriate/have failed/are contraindicated or not tolerated:

- for treating non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis)
- for preventing travellers' diarrhoea or recurrent lower urinary tract infections
- for non-bacterial infections, e.g. non-bacterial (chronic) prostatitis
- for mild to moderate infections (including uncomplicated cystitis, acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease (COPD), acute bacterial rhinosinusitis and acute otitis media).

The dosage forms of the quinolones concerned are both systemic and inhaled ones.

Reference: EMA, 5 October and 16 November 2018
(www.ema.europa.eu)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors – risk of serious infection of the genital area
US-FDA

The US-FDA has recommended that the prescribing information of SGLT2 should include the risk of a rare but serious infection of the genital area. During the period March 2013 to May 2018, 12 cases (7 men, 5 women) of Fournier's gangrene were identified in patients on SGLT2 in USA.

Reference:
Safety Alerts for Human Medical Products, US FDA, 29 August 2018 (www.fda.gov)

Pharmacovigilance & Pharmaceutical Care – a synergistic approach

Medicines and mankind

The multibillion dollar business of medicines is focused towards the objective of curing any ailment in mankind. This field is bustling with new researches being done and new drugs being released on the market. Legislation worldwide has provided a rigid framework to ensure that medical products released on the market have a high safety profile. However, in early 1960s, the thalidomide tragedy gave a terrible shock to the pharmaceutical world and forced Health Professionals to redefine the concept of safety of medicines.

With industrialization catching up on most of the countries not yet in the 'modern era', the economics of the health sector will surely support the fact that the demand for more pharmaceuticals worldwide is creating a boom in that field. A correlation between GDP of a country and expenditure on pharmaceuticals will show that they are directly proportional. Mauritius is following the same pattern and statistics show that a low infant mortality and an increase in life expectancy is somehow related to an increase in use of pharmaceuticals.

Pharmacovigilance, a powerful tool

The World Health Organization defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem. With time, the reason for creating a vigilance system to monitor any Adverse Reaction that might occur with use of medicines, has evolved to encompass other problems that might arise with the use of pharmaceuticals. From a pilot project to a full-fledged International Monitoring Program, Pharmacovigilance has evolved rapidly to be the tool of excellence for Pharmacists to continuously guarantee safety of medicines.

Pharmacists & Pharmacovigilance

Rated as the Health Care Professional (HCP) the most accessible to the patient, Pharmacist has a pivotal role to play in Pharmacovigilance. In every sphere of his activity, he has the professional obligation to ensure that medicines being used are safe for the patients. With the acclaimed importance of Pharmacists in every sector, it is crucial that they also get involved well in Pharmacovigilance.

Pharmacovigilance Pharmacists, also known as the Qualified Persons Responsible for Pharmacovigilance (QPPVs) have a bold presence in the manufacturing sector. Statistics worldwide show the scaring figures of admissions in hospitals due to adverse drug reactions and by extrapolation we do have similar cases in our country. In Mauritius, a strong dynamism has reinvigorated Pharmacovigilance among Hospital Pharmacists.

Perhaps the field where we see much hesitance on behalf of Pharmacists to get involved in Pharmacovigilance is in Retail Pharmacies. The concept of Pharmaceutical Care (PC) revolutionized the way Pharmacists take care of their patients in Pharmacies. One of the pillars of PC is building a relationship of trust between the Pharmacist and the patient. The

newly introduced concept of 'Pharmacien Vigilant' in France incorporates Pharmacovigilance in the day-to-day practice of the Retail Pharmacist and is a core activity if the principle of Pharmaceutical Care is applied. Adequate trust would mean the patients sharing information with their Pharmacists on the positive outcomes of the pharmacotherapy as well as the negative outcomes. Such valuable information could be ADRs and any other data relevant to Pharmacovigilance.

The National Pharmacovigilance Centre in Mauritius wants to encourage Retail Pharmacists to adopt the principle of 'Pharmacien Vigilant' and report any ADR notified to them by their patients.



Community Pharmacists have a very important role to play in the medication cycle of patients. Detecting and reporting ADRs and other drug related problems is part and parcel of the overall responsibility of the Pharmacist in practicing Pharmaceutical Care and achieving drug related outcomes for the patients. With a remarkable figure of 4.1 Pharmacists per 10,000 population in Mauritius, we can provide this service to our community and ensure that we have a good vigilant system overseeing use of medicines.

“Pharmacists should move from behind the counter and start serving the public by providing care instead of pills only. There is no future in the mere act of dispensing. That activity can and will be taken over by the internet, machines, and/or hardly trained technicians. The fact that pharmacists have an academic training and act as health care professionals puts a burden upon them to better serve the community than they currently do.”

(From: Pharmaceutical care, European developments in concepts, implementation, and research: a review)

Last but not least, a CPD was organised by the NPC on Pharmacovigilance for Pharmacists and a Radio Program on public awareness of the NPC and the importance of reporting.



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