PHARMACY BULLETIN

EDITION 16 ISSUE 10 PPUKM 2015

Updates on Cardiac Safety of Domperidone by PRP Asnirah with Ms Izyan

Domperidone, a peripherally selective antagonist of D2 and D3 receptors have been approved in Malaysia to treat nausea, vomiting, dyspepsia and gastrointestinal reflux. Since its registration in 1987, Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) through its vigilant ADR reporting has received reports on its side-effects. Echoing the recent epidemiological studies from European Medicines Agency (EMA) that showed increased risk of serious cardiac adverse effect , National Pharmaceutical Control Bureau (NPCB) has **restricted the indication and dose** recommendation of domperidone. This decision is in line with the risk reduction measures by EMA, Australian Therapeutic Goods Administration (TGA) and Health Canada. Domperidone is not registered in the United States.

Cardiac risks with domperidone have been recognized for many years. The intravenous formulation was withdrawn from the market in 1985 for this reason and it has never been approved in the United States. The European Pharmacovigilance Risk Assessment Committee (PRAC) was asked to examine whether the benefits still outweighed the risks for domperidone in its licensed uses. The PRAC review assessed non-clinical and clinical data, both published and unpublished, and found that there was an increase risk of serious cardiac adverse effect ie **ventricular arrhythmias**, **QTc prolongation, torsade de pointes,** and **sudden cardiac death**. The risk of side-effects were reportedly higher in patients who are either more **than 60 years old**, taking **daily dose of more than 30mg per day** or **co-administered with QT prolong drugs or CYP3A4 inhibitor**.

In Malaysia, there are 25 products containing domperidone registered with Pihak Berkuasa Kawalan Dadah (PBKD) [18 oral products and 7 oral suspension products]. Since year 2000, MADRAC has received 16 reports with 35 adverse reactions on domperidone products. Most of the reports were on urticarial (5 reports), itching (3), rash (3), shortness of breath (2), periorbital oedema (2) and gynaecomastia (2).

Summary of the new recommendation were as below:

Indication :

⇒ For the relief of symptoms of **nausea and vomiting of functional, organic, infectious or dietary origin**.

⇒ **Nausea & vomiting induced by radiotherapy** or drug therapy **dopamine agonists** (L-dopa and bromociptine) used in Parkinson's disease.

Dosage, Administration & Duration :

⇒ Adult , adolescents & weighing above 35kg : 10mg 3-4 times daily by oral (max dose 40mg/day); or 30 mg as a suppository twice a day

⇒ Neonates, infants & children <12yo or body weight <35kg : 0.25mg/kg 3-4 times daily (max: 1mg/kg/day but no more than 35mg)

⇒ Maximum duration of treatment of nausea & vomiting **should not exceed 1 week**.

Contraindication:

⇒ Contraindicated in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure, and when co-administered with QT-prolonging medicines or potent CYP3A4 inhibitors (regardless of their QT-prolonging effects)

Adverse Reactions:

⇒ Postmarketing: Cardiac Disorders such as QTc prolongation, Torsade de Pointes.

In conclusion, patients receiving long-term domperidone should have their therapy reviewed and risks explained to them. It is advisable to use domperidone at the **lowest effective dose** for the **shortest possible duration.** Healthcare professionals are reminded to comply to the new recommendations on metoclopramide and report all adverse drug reactions suspected to NPCB via online reporting [**http://portal.bpfk.gov.my/reporting-healthcare-professional]** or call **03-78835400 (ext 8460/8462/8470).**

ANNOUNCEMENT FROM PHARMACY DEPARTMENT

NEW RECOMMENDATION FOR DRUGS CAUSING SERIOUS SKIN ADVERSE DRUG REACTION by PRP Siew Li

Every year, National Pharmaceutical Control Bureau (NPCB) received thousands of adverse drug reaction (ADR) reports and among them, more than 20% involved the skin. The number of reports has increased substantially since 2009, ranging from the more common ADRs involving the skin such as Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) to less common ones such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. Apart from excruciating and agonizing pain suffered by patients, such ADR prolongs the length of stay in hospital and hence increase the cost of hospitalization as a whole.

In view of this scenario, the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) came up with a recommendation for **WARNING LABELS** to be added on the medications envelope during dispensing. The label served as a reminder to educate patients to be aware of early symptoms of skin reaction, as well as to seek medical advice as soon as possible before the conditions worsen. In their 139-th meeting on 12th June 2014, a proposed warning statement for the 6 pioneer drugs were issued by MADRAC.

The proposals were :

(1) Drugs that can be stopped **IMMEDIATELY**

Allopurinol, Co-trimoxazole, Diclofenac, Mefenamic Acid
If you have side effects such as a rash, fever, sore throat or eye irritation, **STOP using this medication IMMEDIATELY**. Consult your doctor/pharmacist.

(2) Epilepsy drugs that SHOULD **NEVER STOP ABRUPTLY**

Phenytoin, Carbamazepine
If you have side effects such as a rash, fever, sore throat, or eye irritation, **seek medical advice** from your doctor/ pharmacist **IMMEDIATELY**.

Below are the drugs frequently reported to cause serious skin adverse events (source : MADRAC)

Stevens-Johnson Syndrome (SJS)	No	Toxic Epidermal Necrolysis	No	Drug Reaction with Eosinophilia & Systemic Symptoms (DRESS)	No
Allopurinol	197	Allopurinol	28	Allopurinol	53
Carbamazepine	161	Carbamazepine	23	Phenytoin	19
Phenytoin	87	Co-trimoxazole	13	Co-trimoxazole	6
Co-trimoxazole	85	Amoxycillin	12	Dapsone	5
Amoxycillin	43	Diclofenac	12	Isoniazid	5
Diclofenac	30	Phenytoin	10	Pyrazinamide	5
Amoxycillin/clavulanate	21	Mefenamic acid	9	Carbamazepine	4
Cephalexin	21	Cloxacillin	8	Rifampicin	4
Mefenamic acid	21	Traditional medicine	5	Ethambutol	3
Nevirapine	20	Ceftriaxone	4	Nevirapine	3

DRUG SHORTAGE : INJ GLYCOPYRROLATE 0.1mg/mL

Dear doctors,

Please be informed that the manufacturer of Inj Glycopyrrolate 0.1mg/mL (10mL), SM Pharmaceuticals have some problem supplying the drug as their sterile plant is in the midst of validation process with the National Pharmaceutical Control Bureau (NPCB). The supply is expected to resume by **January 2016**. Inj Glycopyrrolate is used in OT as premedication of anaesthetic procedure & reversal of neuromuscular block. For hypersalivation, please consider hyoscine butylbromide.

Thank you.