MADRAC Bulletin

For healthcare professionals only
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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

Articles Based on Case Reports

What's New

We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST). The case reports presented in this section are intended to serve as a reminder of potential adverse events that health care providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.

Clomiphene: Risk of Serious Visual Disturbances

By Goh Pui Yen

Case Report[1]

A 26-year-old female patient took clomiphene 50mg once daily for the treatment of infertility. Two months after therapy initiation, the patient experienced **visual disturbances** in the form of **palinopsia** (prolongation of after images) and **photophobia**. Her palinopsia symptoms occurred at night while her photophobia symptoms occurred upon sudden exposure to light. At the time of reporting, treatment of clomiphene was withdrawn but the outcome of the adverse event was unknown. The adverse events were given a causality *possibly*-related to clomiphene.

Discussion

Clomiphene is classified as a selective oestrogen receptor modulator (SERM) used to treat both female and male infertility.[2-3] It acts by binding competitively to oestrogen receptors, causing decreased binding of endogenous oestrogen. This results in increased secretion of pituitary gonadotropins, which stimulate ovulation in women or the induction of testosterone production and spermatogenesis in men.[2-4] In Malaysia, there are currently four products containing clomiphene registered with the Drug Control Authority (DCA) for the treatment of ovulatory failure in women desiring pregnancy.[5]

The risk of **visual disturbances** has been documented in the local package insert of products containing clomiphene.[6] Visual problems such as blurring, spots, and flashes (scintillating scotomata) may occur especially with increased dosage or prolonged therapy. These symptoms are generally reversible. However, serious visual disturbances which may be irreversible have been reported, including cataracts, optic neuritis, posterior vitreous detachment, retinal haemorrhage, and retinal thrombosis.[7-8]

The mechanism by which clomiphene causes visual problems has not been ascertained. One possible explanation is that clomiphene-use leads to increased blood viscosity due to elevated levels of thrombogenic oestradiol.[2,9] The higher blood viscosity and likelihood of coagulation increase the chances that patients may experience vascular-related events including serious visual disorders.[2] Literature reports indicate that the time to onset for cases of serious visual disturbances leading to blindness is variable, ranging from two days to seven months after initiation of clomiphene treatment.[2,7,10] This adverse event may be irreversible, as illustrated in a case report by Alizadeh *et al.* (2021), where the patient experienced persistent visual defects three months after discontinuation of clomiphene.[2]

Figure 1. *Example of palinopsia with a moving object (the hand is moving from left to right), leaving behind a trail of afterimages.*[11]

To date, NPRA has received 15 adverse drug reaction (ADR) reports with 25 adverse events suspected to be related to clomiphene.[1] The most frequently reported adverse events were dizziness (2), urticaria (2), and abdominal pain (2). In addition to the local case report of palinopsia and photophobia discussed above, NPRA also received **one report of blurred vision** suspected to be related to clomiphene.[1]

As of March 2024, a search of the World Health Organisation (WHO) global ADR database[12*] revealed a total of 627 adverse events classified as eye disorders suspected to be associated with clomiphene. The top reported events were visual impairment (57.4%) and vision blurred (11.2%), while there were 13 reports on blindness (2.1%).

This safety issue was highlighted by the France National Agency for the Safety of Medicines and Health Products (ANSM) in June 2023.[13] ANSM reviewed the association of clomiphene with the risk of serious visual disturbances potentially leading to blindness, and concluded that clomiphene product information should be updated with this risk.[14] NPRA is currently evaluating the need to update all clomiphene- containing products with information on the risk of serious visual disturbances leading to blindness (see also the safety alert on the NPRA website).

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Healthcare Professionals

1. Be aware of the risk of serious and possibly irreversible visual disturbances associated with clomiphene use.
2. Before starting treatment with clomiphene, a detailed ophthalmic examination should be performed. Regular ophthalmic examinations should also be conducted on patients throughout the duration of clomiphene therapy.
3. Counsel patients and caregivers on the possible risk of vision problems following clomiphene administration particularly with the use of higher doses or longer duration of treatment. Patients should discontinue clomiphene treatment immediately and seek medical attention if they experience any visual disturbances.
4. Report all suspected adverse events associated with clomiphene-containing products to the NPRA.

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Domperidone: Risk of Seizures

By Ng Wan Ning

Case Report 1 [1]

Note: In May 2020, NPRA issued a directive that domperidone should not be used in infants and children less than 12 years of age who weighs less than 35 kg.[2] The case report illustrated here was received prior to issuance of the directive.

A 3-year-old female patient presented to the emergency department with two episodes of vomiting. She was treated with oral rehydration salts, paracetamol, domperidone, and ranitidine. She was given two doses of domperidone syrup (2mg at 5pm and 10pm respectively). The following night, the patient experienced a total of **five episodes of fitting** with staring look, each lasting about 5-10 seconds. She was reported to have recovered from this adverse event. In view of the potential presence of confounding factors over an extended period and concomitant drugs, a causality of *possible* was assigned for this case.

Case Report 2 [1]

A 72-year-old male patient with underlying ischemic heart disease was given domperidone 10mg three times daily to treat bloated feeling and abdominal pain associated with constipation. About 30 minutes after taking the medication, he experienced itchiness on his back and excessive sweating. Then the patient had uprolling of eyeballs and jerky movement of his bilateral upper and lower limbs. The seizure lasted for 10 seconds and aborted spontaneously. The patient was noted to have post-ictal drowsiness when he arrived at the emergency department. He was diagnosed with **resolved anaphylactic shock secondary to domperidone, and fitting secondary to anaphylactic shock**. The patient was treated with intramuscular adrenaline and intravenous hydrocortisone. He was reported to have recovered from the adverse event. The causal relationship of the observed adverse event has been assessed as *possible*.

Discussion

Domperidone is indicated for the relief of symptoms of nausea and vomiting.[3] Domperidone is a dopamine antagonist thought to exert its antiemetic effect through a combination of gastrokinetic effects as well as antagonism of dopamine receptors in the gut and the chemoreceptor trigger zone. In Malaysia, there are currently 16 registered products containing domperidone, which are available in the form of tablets (11) and suspensions (5).[4] Since 2015, NPRA has implemented several regulatory measures to reduce the cardiovascular risks associated with domperidone use.[5]

Image created by OpenAI's DALL-E

The term "**convulsion**" is documented as a very rare adverse event (frequency <1/10,000) associated with domperidone use.[3] Studies have reported that administration of high doses of domperidone is linked with increased risk of seizures, though the exact mechanism is not known.[6,7] The increased risk of central effects among paediatric patients is most likely due to their underdeveloped blood-brain barrier.[8]

To date, NPRA has received 70 ADR reports with 134 adverse events associated with domperidone use.[1] The most commonly reported adverse events were urticaria (14), pruritus (13), rash (11), periorbital oedema (5) and face swelling (5). At the time of publication, NPRA has received **three reports of seizure** (including the two cases described above) which were associated with domperidone use. Time to onset of seizure was reported to be between seconds to one day, and all three patients recovered from the adverse event after drug withdrawal.[1] As this reaction is very rare, its occurrence may be overlooked and under-reported.

Based on the WHO global ADR database, as of March 2024, there were a total of 14,356 adverse events associated with domperidone use.[9*] Among these, there were 128 cases of seizure involving 65 children and 50 adults, while 13 cases did not specify the age group.

*DISCLAIMER

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Advice for Health Care Professionals

1. Be vigilant on the possible risk of seizures with domperidone use.
2. Counsel patients and their caregivers that domperidone may cause seizures. Advise patients to seek urgent medical attention if they have uncontrolled or unusual movement of their limbs or eyes.
3. Reminder: Domperidone should not be used in infants and children less than 12 years of age who weigh less than 35 kg.
4. Domperidone should be used at the lowest effective dose for the shortest duration possible. The usual maximum treatment period should not exceed one week.
5. Please report any adverse events associated with domperidone to the NPRA

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What's New

List of Safety Alerts/Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Statins (Atorvastatin, Rosuvastatin, Simvastatin)	Interaction with Ticagrelor Leading to Increased Risk of Rhabdomyolysis	19-Feb-2024	-
2	Metformin	[Updated] Risk of Vitamin B12 Deficiency	04-Mar-2024	NPRA.600-1/9/13(32) Jld.1 [16 Jan 2024]
3	Domperidone	Risk of Psychiatric Withdrawal Events When Used Off-Label for Lactation Stimulation	12-Mar-2024	-

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit www.npra.gov.my
2. Report ADR as Healthcare Professional
   a) Choose Online Reporting or
   b) Download the ADR manual form and submit the completed form via email or post:

fv@npra.gov.my

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NPRA Safety Information Mailing List

To join the mailing list:

a) scan the QR code to complete the subscription form, or

b) send an email with your details to fv@npra.gov.my