



MADRAC *Newsletter*

For healthcare professionals only

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Features

Cyclopentolate Eye Drops Use in Premature Infants: Risk of Respiratory Adverse Events

by *Wo Wee Kee*

Background of the safety issue

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of retinal vasculature in low birth weight premature infants. It can be mild with no visual defects, or it may become aggressive, progressing to retinal detachment and blindness. ROP screening should be done 4 to 6 weeks after birth and continue every 1-3 weeks depending on the progression of disease^{1,3}.

Mydriatic eye drops, either parasympathetic blockers or sympathetic stimulants, are used to dilate the pupils before ROP eye examination. Anticholinergic agents (e.g. cyclopentolate) produce dilation of the pupil (mydriasis) and paralysis of accommodation (cycloplegia) via

inhibition of acetylcholine action on the sphincter muscle and ciliary muscle of the lens. Sympathetic agents (e.g. phenylephrine) act on adrenergic receptors in the eye producing contraction of pupillary dilator muscle. Generally, for maximum dilation and minimum side effects, a combination of these agents are used for ROP screening.

Registered Products in Malaysia

There are five (5) products containing cyclopentolate registered in Malaysia, of which four contain cyclopentolate 1% as the single active ingredient, and one is a combination product containing cyclopentolate 0.2% and phenylephrine 1%.

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Local Adverse Drug Reaction (ADR) reports

From year 2000 until December 2016, the NPRA received 62 reports with 97 adverse events suspected to be related to products containing cyclopentolate (44 reports for combination cyclopentolate/ phenylephrine, and 18 reports for the single active ingredient).

Respiratory disorders contributed the most reports (39 reports, 63%) with 43 adverse events, followed by cardiovascular adverse events (cyanosis, bradycardia), and gastrointestinal adverse events (abdominal distension).

The respiratory adverse events reported were apnoea, decreased oxygen saturation, respiratory distress, bronchospasm, dyspnoea, tachypnoea and sleep apnoea. All were reported to occur in infants aged 3 months or less. The time to onset of reaction ranged from one (1) minute to less than one day. About 49% of the reports had an onset of less than 4 hours, while a further 15% of the reactions were reported to occur between 4 to 12 hours after the administration of the eye drops in infants².

Other possible causes for respiratory adverse events

Respiratory disorders are a common complication in premature infants. Among the cases mentioned above, there were eight (8) patients with underlying apnoea of prematurity/respiratory distress syndrome, one (1) with bronchopulmonary dysplasia, and one (1) with asthma. These underlying conditions may have contributed to the reported respiratory adverse events.

The International Evidence-Based Group for Neonatal Pain has included ROP screening

examination in the list of painful procedures performed in the NICU. This stressful procedure may also result in harmful physiological changes including bradycardia and decreased oxygen saturation³⁻⁵.

Compression of the eyeball using a sclera depressor during the eye examination may also stimulate the oculocardiac reflex, which in turn causes apnoea and bradycardia. However, the physiologic responses associated with eye examinations are immediate³. Since some of the respiratory events reported in Malaysia were delayed, this suggests the possibility of other causes.

Regulatory Action

The current package insert for cyclopentolate-containing products states that infants should be observed closely for at least 30 minutes following instillation. Based on the review of our local ADR reports, the NPRA has called for amendment of the 'Warnings & Precautions' section as follows: **Observe infants closely for at least one (1) day following instillation.**

References

1. Retinopathy of prematurity (2005). Clinical Practice Guidelines. Ministry of Health Malaysia.
2. National Adverse Drug Reaction database, NPRA. [Accessed: November 2016]
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5. Kirchner L, Jettler V, Pollak A, et al. (2009). Must screening examinations for retinopathy of prematurity necessarily be painful? *Retina*. 29: 586-591.

Advice to Healthcare Professionals

- It is recommended to use the minimum possible concentrations and doses of mydriatic eye drops to achieve effective mydriasis and minimise the risk of systemic absorption.
- Infants are especially prone to the side effects from systemic absorption of cyclopentolate.
- Observe infants closely for at least **one (1) day** following instillation of cyclopentolate-containing eye drops.
- Please report any ADRs suspected to be related to the use of cyclopentolate-containing eye drops to the NPRA.

Features

Colchicine: Reminder on the Risk of Toxicity

by Wang Khee Ing

Background of the safety issue

In November 2016, the NPRA received information from the French National Agency for Medicines and Health Products Safety (ANSM) regarding cases of colchicine dosing error and overdose¹. A Dear Healthcare Professional Communication (DHPC) letter was issued in France as a reminder on the risk of serious overdose with colchicine following the occurrence of new cases of serious adverse reactions (some fatal) associated with an overdose of colchicine.

About the medicine

Colchicine is indicated for the treatment of acute gout, as an alternative drug for patients in whom non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are not tolerated or ineffective². It is also licensed for short-term prophylaxis of gout flares during initial therapy with urate-lowering treatment.

Colchicine works by inhibiting neutrophil migration, chemotaxis, adhesion and phagocytosis in the area of inflammation. While it reduces the inflammatory reaction to urate crystals, it does not affect the production and excretion of uric acid³.

As colchicine has a narrow therapeutic index, there is a significant risk of toxicity if it is not used correctly. The first stage of colchicine toxicity includes gastrointestinal (GI) symptoms such as abdominal pain, nausea, vomiting, and diarrhoea. This usually begins within 24 hours of ingestion⁴. The appearance of GI symptoms before **signs of more serious toxicity** provides a margin of safety in colchicine use. **Colchicine should be discontinued if these GI symptoms occur** and should not be restarted until these symptoms disappear, which is normally within 24-48 hours.

Local Scenario

In Malaysia, there are currently three (3) products containing colchicine registered with the Drug Control Authority (DCA). Since year 2000, the NPRA has received 64 ADR reports

with 120 adverse events suspected to be related to colchicine. The most commonly reported ADRs were diarrhoea (19, 15.8%), itching (10, 8.3%), rash (9, 7.5%), and pruritus (8, 6.7%).

Among these 64 reports, there were two (2) cases (3.1%) related to fatal overdose. The first case reported **prolonged diarrhoea for a month** in a 70 year-old man who took colchicine 0.5mg tds for 37 days. This patient had underlying gouty arthritis for 10 years with infrequent attacks. The reported cause of death was **sepsis with underlying acute on chronic renal failure secondary to colchicine overdose**. He was on concomitant medication which may have contributed to the adverse event; therefore the case was assigned causality C3 (possibly-related to the drug).

The second case reported **severe diarrhoea and vomiting associated with colchicine-use in a patient with underlying renal impairment**. This 46 year-old female took colchicine 0.5mg OD for 15 days. The patient also had underlying diabetes, hypocortisolism, hyperlipidemia, and multiple joint pain on and off. The cause of death was **severe pneumonia with multiorgan failure**. She was also on multiple concomitant medications; hence the case was assigned causality C3. During further investigation, it was discovered that the patient continued taking colchicine despite suffering vomiting and profuse diarrhoea for about 15 days.

While the package inserts of colchicine products in Malaysia already include advice to discontinue the medication if GI symptoms occur⁵, the NPRA would like to emphasise the importance of effective counselling to minimise the risk of toxicity.

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References

1. French National Agency for Medicines and Health Products Safety (ANSM) Vigilance Bulletin, number 71, Nov 2016.
2. Clinical Practice Guidelines Oct 2008.
3. Safer prescribing of high-risk medicines: Colchicine – extremely toxic in overdose, Best Practice Journal Issue 63, Sept 2014, P.58-60.
4. Colcrys (Colchicine, USP) tablets, for oral use US Prescribing Information, revised 12/2015.
5. Tolchicine Tablet, Malaysian Package Insert, revised 5/2010.

Advice to Healthcare Professionals

- The recommended dosage regimen should be followed to reduce the risk of toxicity due to the narrow therapeutic index of colchicine.
- Strictly comply with the approved indications of colchicine and always evaluate the benefit:risk ratio of colchicine before prescribing it to a patient.
- Adjust dosage in the elderly, and patients with renal failure or liver failure. These patients should be closely monitored.
- Verify that there is no risk of drug interactions and contraindications with P-glycoprotein or strong CYP3A4 inhibitors (e.g. ketoconazole, calcium channel blocker and macrolides such as EES).

Counselling Points

- Stop taking colchicine and seek immediate medical attention if you experience abdominal pain, profuse diarrhoea, nausea, vomiting, or burning feeling in the throat, stomach or skin.
- Colchicine is not a general analgesic and is NOT to be used to manage pain other than due to gout.
- Inform your doctor or pharmacist about all medications you are taking, and always check with them before taking any new medications.
- Ensure all medications are stored safely out of reach of children.

Features

Summary of Safety Concerns Linked to Dipeptidyl Peptidase (DPP)-4 Inhibitors

by Ng Chiew Seng

Dipeptidyl peptidase-4 (DPP-4) inhibitors, or the 'gliptins', belong to a class of oral antidiabetic drugs that are used alone or along with other antidiabetic agents, as an adjunct to diet and exercise. Inhibition of the enzyme DPP-4 temporarily stops the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic hormone (GIP) at the gastrointestinal tract, thereby prolonging the effects of GLP-1 and GIP. Both GLP-1 and GIP cause a glucose-dependent increase in insulin secretion, and GLP-1 also contributes to glucose homeostasis by exerting effect on insulin biosynthesis and inhibiting glucagon release. This, in turn, leads to a net antihyperglycaemic effect.

Currently, there are 22 products containing DPP-4 inhibitors (namely sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) available in Malaysia. These are found as single-ingredient products and in combination with metformin.

The DPP-4 inhibitors have been linked to several different safety issues in recent years, as described below. While a causal relationship has not been established with some of the adverse drug reactions (ADRs) below, the NPRA would like to highlight the current information available in order to increase awareness among healthcare professionals and stimulate ADR reporting.

1 Severe Joint Pain (Arthralgia)

This issue was previously featured in [Bulletin MADRAC December 2015](#).

In August 2015, the NPRA received a safety alert from the United States Food and Drug Administration (US FDA) on the risk of DPP-4 inhibitors causing joint pain that can be severe and disabling. The FDA review of their Adverse Event Reporting

System database identified 33 cases of severe arthralgia suspected to be related to the use of DPP-4 inhibitors reported between October 2006 (when the first DPP-4 inhibitor was approved) to December 2013. Analysis of the reports revealed that patients started to have symptoms of joint pain anywhere from one day to years after they started taking the drugs.

Ten (10) of the cases reported patients requiring hospitalisation, and upon discontinuation of the medicine, symptoms normally resolved in less than a month. When restarted on the same drug or a different DPP-4 inhibitor, some patients experienced a recurrence of symptoms¹. The US FDA has added a Warning and Precaution related to this risk in the package inserts of all DPP-4 inhibitors.

Locally, there were three (3) ADR reports related to joint pain involving sitagliptin. All three cases were given causality C3 (possibly-related to drug). For more details on these cases, please refer to [Bulletin MADRAC December 2015](#).



two large clinical trials of saxagliptin and alogliptin conducted in patients with heart disease. Each trial showed that more patients who received saxagliptin or alogliptin containing medicines were hospitalised for heart failure compared to placebo⁴. As a result of this review, new warnings were added to the labels of medicines containing saxagliptin or alogliptin to inform of the potential increased risk of heart failure.

Locally, the NPRA database contains one (1) report related to heart failure involving vildagliptin. This case was given causality C4 (unlikely-related to drug) due to the improbable time-relationship with drug intake. The patient was reported to have developed heart failure after taking just one dose of vildagliptin/metformin combination product.

2 Pancreatic Carcinoma/ Pancreatitis

In February 2014, the US FDA and the European Medicines Agency (EMA) published a scientific article which concluded that a link between incretin-based therapies and pancreatitis/ pancreatic cancer could not be made based on data at hand. Both agencies continue to investigate this safety signal².

In October 2016, a review by Health Canada on this safety issue also concluded that there is currently **insufficient evidence** to link incretin-based therapies with pancreatic cancer. Although some non-clinical studies using animal or human models have suggested that the use of incretin-based therapies may be linked to an increased risk of pancreatic cancer, results from clinical trials and many studies looking at the patterns, causes, and effects of health and disease conditions in people, do not support this link³.

Locally, NPRA received one (1) report of pancreatic carcinoma and five (5) reports of pancreatitis suspected to be associated with sitagliptin-use. All six cases were given causality C3 (possibly-related to drug).

3 Heart Failure

In February 2014, a review by the US FDA found that saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients with underlying heart or kidney disease. The review involved evaluation of

4 Pemphigoid

Cases of pemphigoid were reported among patients treated with linagliptin, alogliptin and teneligliptin in Japan. In November 2016, following a review of expert advisors opinions and the available evidence, the Pharmaceuticals and Medical Devices Agency (PMDA), Japan concluded that the package inserts of these products should be revised with the addition of "Pemphigoid" under Clinically Significant Adverse Reactions⁵.

In Europe, 'pemphigoid' is currently documented in the product information for sitagliptin and linagliptin. EMA required vildagliptin-containing products to be updated with the inclusion of 'pemphigoid' under 'Undesirable Effects' after having considered the available evidence from case reports in EudraVigilance and in the literature, including the disproportionality score for vildagliptin being the highest of the DPP-4 inhibitor class⁶. There was insufficient

evidence at this time to support extension of this signal throughout the DPP-4 inhibitor class.

Locally, there has been no pemphigoid case reported to the NPRA to date.

5 Gastrointestinal Obstruction

In November 2016, Health Canada carried out a safety review on the potential risk of gastrointestinal obstruction with the use of DPP-4 inhibitors. This was triggered by international reports of gastrointestinal obstruction in patients using sitagliptin, and the review was then extended to include all DPP-4 inhibitors available in Canada (namely sitagliptin, saxagliptin, linagliptin and alogliptin).

The review assessed 40 reports (39 international and 1 Canadian) of gastrointestinal obstruction in patients who used a DPP-4 inhibitor. Of these, 11 international reports [involving sitagliptin (6), alogliptin (3) and linagliptin (2)] showed a possible link between the drug and

gastrointestinal obstruction, however all these cases also identified other potential causes of the gastrointestinal obstruction. Health Canada concluded that there is currently insufficient information available to confirm a link between use of DPP-4 inhibitors and gastrointestinal obstruction⁷.

Locally to date, the NPRA has not received any report of gastrointestinal obstruction related to gliptin-use.

References

1. FDA Drug Safety Communication (2015). FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain.
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3. Health Canada Summary Safety Review (2016). Incretin-Based Therapies - Assessing the Potential Risk of Pancreatic Cancer.
4. FDA Drug Safety Communication (2014). FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin.
5. PMDA (2016). Summary of investigation results: Alogliptin benzoate-containing drugs, Linagliptin, Teneligliptin hydrobromide hydrate.
6. EMA (2016). PRAC recommendations on signals adopted at the PRAC meeting of 28 November-1 December 2016.
7. Health Canada Summary Safety Review (2016). DPP-4 inhibitors (gliptins) - Assessing the Potential Risk of Gastrointestinal Blockage (Gastrointestinal Obstruction).

Advice to Healthcare Professionals

- Advise patients to seek immediate medical attention if they experience severe and persistent joint pain. DPP-4 inhibitors should be considered as a possible cause for severe persistent joint pain, and the drug should be discontinued if appropriate.
- Be aware and monitor for the signs and symptoms of pancreatitis (nausea, vomiting, anorexia, and persistent severe abdominal pain, sometimes radiating to the back). Discontinue DPP-4 inhibitors if pancreatitis is suspected. Understand that if pancreatitis is suspected, supportive medical care should be instituted. The patient should be monitored closely with appropriate laboratory studies (serum and urine amylase, amylase/ creatinine clearance ratio, electrolytes, serum calcium, glucose, and lipase.)
- Advise patients to contact their health care professionals right away if they develop signs and symptoms of heart failure such as unusual shortness of breath during daily activities, trouble breathing when lying down, tiredness, weakness, or fatigue, weight gain with swelling in the ankles, feet, legs, or stomach.
- Tell patients to contact their health care professionals if they develop blisters or erosions while receiving DPP-4 inhibitors. If bullous pemphigoid is suspected, DPP-4 inhibitors should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.
- Please report any ADRs suspected to be related to the use of DPP-4 inhibitors to the NPRA.

Regulatory Matters

Levonorgestrel-Containing Emergency Hormonal Contraception: New Advice on Interactions with Hepatic Enzyme Inducers and Contraceptive Efficacy

The NPRA would like to highlight new safety information related to the use of levonorgestrel-containing emergency hormonal contraception.

It is a known fact that the metabolism of levonorgestrel is increased by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. New information has quantified the interaction with the antiretroviral, efavirenz, showing that concomitant administration reduces the plasma levels (AUC) of levonorgestrel by around 50%. Based on extrapolation from studies involving combined oral contraceptives, other hepatic enzyme inducers may produce similar reductions in plasma levels of levonorgestrel. This reduction in plasma level may decrease the contraceptive efficacy of levonorgestrel-containing emergency hormonal contraceptives.

Women who are using or have used enzyme-inducing drugs during the last four (4) weeks and need emergency contraception should consider the use of non-hormonal emergency contraception, namely a copper intrauterine device (Cu-IUD). Those unable or unwilling to use a Cu-IUD should take a double dose of levonorgestrel. There is no expected increased risk of side effects with the use of the higher dose in these circumstances.

Local Scenario

There are currently seven (7) levonorgestrel-containing emergency contraceptive products registered in Malaysia. At the time of this publication, the NPRA has not received any ADR report related to these products.

All product package inserts are required to be updated with this new dosing recommendations related to the drug interaction, as stated in the Malaysian Drug Control Authority (DCA) directive dated 29 May 2017 [[Ref: \(16\) dlm.BPFK/PPP/07/25 Jilid 1](#)] which may be downloaded from the NPRA website.

Direct Healthcare Professional Communication (DHPC) letters have also been issued by the product registration holders in agreement with NPRA, to highlight this new information.



Advice to Healthcare Professionals

- Advise women requiring emergency contraception who have used an enzyme-inducing medicine within the last four (4) weeks to use a non-hormonal emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD).
- Those who are unable or unwilling to use a Cu-IUD should be advised to double the usual dose of levonorgestrel from 1.5 mg to 3 mg to compensate for the reduction in plasma levonorgestrel levels.
- Please report any adverse reactions suspected to be related to the use of levonorgestrel-containing emergency hormonal contraception, particularly associated with the use of a double dose.

What's New?

Reaching Out to the Public

In the past, most of the communication from NPRA has been targeted to healthcare professionals and pharmaceutical companies. Now we are focusing extra effort on increasing communication to the general public on issues related to medication safety.

In November 2016, two television interviews with RTM and TV Al-Hijrah were conducted, aiming to increase public awareness on medication safety. Topics covered included: what are ADRs or side effects, what to do if you experience a side effect, how to report ADRs, why it is important to report, and the role of NPRA in monitoring drug safety in Malaysia.

Stay tuned for more appearances this year!



For Healthcare Professionals

How to report adverse drug reactions?


NPRA encourages the reporting of all suspected adverse drug reactions to medicines, including vaccines, over-the-counter medicines, traditional products and health supplements.


To report an adverse drug reaction:

1. Visit nptra.moh.gov.my
2. Click on [ADR Reporting](#)
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Completed forms may be submitted via email, post or fax to:

 The Pharmacovigilance Section,
National Pharmaceutical Regulatory Agency (NPRA),
Ministry of Health, Malaysia,
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