

MADRAC *Newsletter*

For healthcare professionals only

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Regulatory Matters

Chlorhexidine preparations: Risk of hypersensitivity reactions

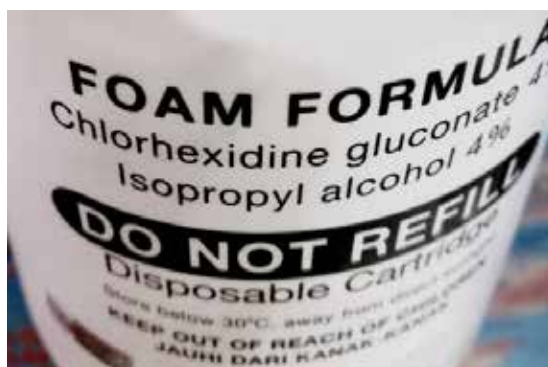
by Ng Chiew Seng

Background of the safety issue

Chlorhexidine is a synthetic bis-biguanide which is widely used as a disinfectant in the medical and surgical fields. Chlorhexidine is highly valued due to its low cost and microbicide properties towards a wide range of microorganisms. Unfortunately, it may cause hypersensitivity reactions, ranging from contact dermatitis to life-threatening anaphylaxis.

Due to its allergenic properties, chlorhexidine may potentially complicate a perioperative or anaesthetic session. However, its role as an allergen is often undervalued and misdiagnosed¹.

Topically-applied chlorhexidine is usually well-tolerated with limited systemic absorption. However, when applied on burnt skin, minor excoriations or even small open wounds, there is an increased risk for chlorhexidine-triggered anaphylaxis. Anaphylactic reactions have been



also reported in individuals with healthy skin, as alcoholic solutions of chlorhexidine may cause dehydration of stratum corneum proteins. This may potentially increase the permeation of chlorhexidine into the dermal skin compartment and cause allergic reactions¹.

NPRA received information from Health Canada regarding hypersensitivity reactions associated with chlorhexidine-containing topical products. Health Canada's safety review determined that topical chlorhexidine may cause serious

anaphylactic reactions in certain conditions when used in the mouth, on open wounds, or immediately before or during surgery². Besides Health Canada, the United States Food and Drug Administration (US FDA) has issued a warning on the risk of serious allergic reactions with the use of skin antiseptic products containing chlorhexidine³.

Registered Products in Malaysia

In Malaysia, there are currently 47 products containing chlorhexidine registered with the Drug Control Authority (DCA), in various dosage forms such as creams, lotions, gels, scrubs, solutions, mouthwashes and lozenges.

Local ADR Reports

NPRA has received 29 reports with 55 adverse events suspected to be related to products containing chlorhexidine.

Majority of the adverse events (21 events, 38%)

involved skin and subcutaneous tissue disorders such as rash, pruritus and skin irritation. Among the 29 reports, there were **four (4) cases** of anaphylaxis/anaphylactic shock following the use of topical chlorhexidine products. The time to onset of anaphylaxis/anaphylactic shock ranged from 10 to 30 minutes. All cases were assigned causality C3 (possibly-related to the drug) except for one (1) case, causality C1 (certain to be related to the drug) was given as specific immunoglobulin E (IgE) to chlorhexidine detection, skin prick test and intradermal test all showed positive results.

Regulatory Action

NPRA has reviewed this safety issue and a directive [Ref: (13) dlm. BPFK/PPP/07/25 Jilid 1] was issued for all local package inserts and labels of products containing chlorhexidine to be updated with information on the risk of hypersensitivity reactions.

Advice to Healthcare Professionals

- Serious allergic reactions, including fatal anaphylaxis, have been reported with chlorhexidine. These reactions can occur within minutes of exposure, and can occur with topical or oral exposure to the drug.
- Symptoms of a serious allergic reaction, including anaphylaxis, may include itchy hives with swelling of the face, eyes, lips, mouth or throat; difficulty breathing; throat tightness or hoarseness; and fainting.
- If a patient exhibits an unexplained allergic reaction prior to or during surgical procedure, check whether chlorhexidine was used.
- If you suspect a patient may have (or has had) an allergic reaction to chlorhexidine, monitor the reaction carefully, provide immediate respiratory and/or cardiovascular support as needed, and discontinue use of the drug or medical device containing chlorhexidine as soon as possible.
- Always ask patients if they ever had a reaction to the ingredient or to any antiseptic products, prior to using chlorhexidine.
- Consider using alternative antiseptics such as povidone-iodine or alcohol when any previous allergy to chlorhexidine is documented or suspected.
- Please report any ADR suspected to be related to chlorhexidine use to the NPRA.

References

1. Calogiuri, GF et al (2013). Chlorhexidine Hypersensitivity: A Critical and Updated Review. *Journal of Allergy & Therapy* 4:4.
2. Health Canada Summary Safety Review (2016). Topical Antiseptic Non-Prescription Chlorhexidine Products - Assessing the Potential Risk of Serious Allergic Reactions (Hypersensitivity Reactions).
3. FDA Drug Safety Communication (2017). FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate.
4. The National ADR Database, NPRA [Accessed July 2017].

Regulatory Matters

Miconazole & Warfarin: Risk of severe bleeding as a result of drug interaction

by Ng Chiew Seng

Background of the safety issue

Miconazole is an azole antifungal indicated for prevention and treatment of various infections of the mouth, skin, nails or genitals, whereas warfarin is an anticoagulant that has been widely used for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as prevention of thromboembolic complications¹.

Although precautionary information regarding the risk of bleeding due to interaction between miconazole and warfarin has been provided in the package insert of miconazole, serious cases of bleeding with co-administration of these drugs continue to be reported. This has prompted the Pharmaceuticals and Medical Devices Agency (PMDA), Japan to contraindicate the co-administration of miconazole (oral gel and injection formulations) and warfarin.

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) has also published a reminder to healthcare professionals in their monthly Drug Safety Update bulletin about this potential drug interaction¹. In addition, the French National Agency for Medicines and Health Products Safety (ANSM) extended the contraindication for co-administration of warfarin with all routes of administration for miconazole³.



Possible Mechanism of Action

Warfarin occurs as a pair of enantiomers that are differentially metabolised by human cytochromes (CYP) P450. R-warfarin is metabolised primarily by CYP1A2 to 6- and 8-hydroxywarfarin, by CYP3A4 to 10-hydroxywarfarin, and by carbonyl reductases to diastereoisomeric alcohols. S-warfarin is metabolised primarily by CYP2C9 to 7-hydroxywarfarin. The efficacy of warfarin is affected primarily when metabolism of S-warfarin is altered⁴.

The potential for drug interaction between miconazole and warfarin is well established. The mechanism is thought to be through the inhibition of CYP2C9 by miconazole, resulting in reduced warfarin clearance and an enhanced anticoagulant effect¹.

Registered Products in Malaysia

In Malaysia, there are currently 43 products containing miconazole registered with the Drug Control Authority (DCA), in various dosage forms such as cream, ointment, powder, lotion, tincture, pessary and oral gel. To date, there is no miconazole injection registered locally. For warfarin, a total of five (5) products are registered at present.



Local ADR Reports

NPRA has received 34 reports with 51 adverse events suspected to be related to products containing miconazole. Majority of the adverse events (38, 75%) involved skin and subcutaneous tissue disorders such as rash, pruritus and contact dermatitis. At present, no reports of increased INR or severe bleeding due to concomitant use of miconazole and warfarin have been received locally⁵.

Regulatory Action

The product package inserts and patient information leaflets of all registered products containing miconazole and warfarin are required to be updated with information related to this risk of drug interaction. Two directives on this matter have been issued on 29 May 2017 [*Ruj: Bil (15) dlm. BPFK/PPP/07/25 Jld. 1*] and [*Ruj: Bil (17) dlm. BPFK/PPP/07/25 Jld. 1*], which are available on the NPRA website.

Advice to Healthcare Professionals

- The co-administration of miconazole oral gel with warfarin is now **CONTRAINDICATED**.
- If other topical dosage forms of miconazole are used concurrently with warfarin, caution should be exercised and the anticoagulant effect should be monitored.
- Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using products that contain miconazole, and to seek medical attention if they experience any signs of bleeding during treatment, such as sudden unexplained bruising, nose bleeds or presence of blood in the urine.
- Please report any ADRs suspected to be related to the use of miconazole and/or warfarin to the NPRA.

References

1. MHRA Drug Safety Update (2016). Topical Miconazole, Including Oral Gel: Reminder of Potential for Serious Interactions with Warfarin.
2. PMDA Safety Information (2016). Interactions in Co-administration of Miconazole and Warfarin Potassium.
3. ANSM GT Interactions médicamenteuses du - Compte-rendu GT102016033 (2016).
4. Kaminsky, LS & Zhang, ZY (1997). Human P450 Metabolism of Warfarin. *Pharmacol Ther* 73(1):67-74.
5. The National ADR Database, NPRA [Accessed July 2017].

Inhaled Corticosteroids: Increased risk of pneumonia in Chronic Obstructive Pulmonary Disease (COPD) patients

by Wan Noor Ardila Wan Abhar

Pneumonia is an identified risk in patients on inhaled corticosteroid (ICS) therapy¹. The pathogenesis of increased pneumonia with ICS is unclear, however, it is possible that ICS can alter local immune mechanisms in the airways².

Background of the safety issue

The signal of increased risk of pneumonia in COPD patients with use of ICS was first identified in the TOwards a Revolution in COPD Health (TORCH) study in 2007. This was a double-blind comparative study to assess the safety and efficacy of fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. Since then, other products containing ICS have been subjected to review for this risk.

In order to further characterise this risk in

the COPD patient population, the Pharmacovigilance Risk Assessment Committee (PRAC) from the European Medicines Agency (EMA) reviewed the data on all ICS products in this population and confirmed that COPD patients treated with ICS are at increased risk of pneumonia³. However, PRAC's view is that the benefits of ICS continue to outweigh their risks. PRAC also concluded that there is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among products containing ICS. Asthmatic patients on similar inhaled corticosteroid therapy, however, were not included in this review.

In view of all collectible findings, PRAC concluded that pneumonia (in COPD patients) should be added as a common adverse reaction in the product information for all products containing ICS.



Registered Products in Malaysia

There are currently 38 products containing ICS (as a single drug or combination formulations) registered for the management of COPD in Malaysia. These products include the following active substances: budesonide*, fluticasone*, budesonide/formoterol fumarate, fluticasone propionate/salmeterol, fluticasone furoate/vilanterol trifenate and beclomethasone dipropionate/formoterol.

Local ADR Reports

Since year 2000, the NPRA has received 28 reports with 44 adverse events related to ICS use for the management of COPD. The most commonly reported adverse events are

coughing, nausea, headache and throat irritation. To date, NPRA has not received any ADR reports relating to pneumonia with ICS-use for the management of COPD.

Regulatory Action

NPRA has reviewed this safety issue and a directive [Ref: (14) dlm. BPFK/PPP/07/25 Jilid 1] was issued for the local package inserts of all products containing budesonide (single and combination formulation), fluticasone (single and combination formulation) and beclomethasone (combination formulations only) to be updated with new warnings on the increased risk of pneumonia in COPD patients.

*These products are indicated for asthma, however, current clinical practice guidelines have recommended the use of these products in combination with short-acting beta agonists/short-acting acetylcholinergic agents for the management of COPD.

Advice to Healthcare Professionals

- As the clinical features of pneumonia overlap with those of exacerbations of COPD, healthcare professionals are advised to be vigilant for signs and symptoms of pneumonia in these patients.
- Patients should be advised to report any increased breathing difficulties such as an exacerbation with other symptoms suggestive of infection (e.g. fever, chills, increased amount of mucus, change in mucus colour and worsening of cough).
- All healthcare professionals are encouraged to report any adverse reactions suspected to be related to the use of ICS to the NPRA.

References

1. Calverley et al. (2007). Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. The New England Journal of Medicine, Vol. 356 No. 8.
2. Calverley et al. (2009). Pneumonia risk in COPD patients receiving inhaled corticoids alone or in combination: TORCH study results. EUR Respir J 2009; 34: 641-647.
3. EMA (2016). EMA completes review of inhaled corticosteroids for chronic obstructive pulmonary disease (EMA/285392/2016).
4. The National ADR Database, NPRA [Accessed June 2017].

Regulatory Matters

Etoricoxib: New dosing for rheumatoid arthritis and ankylosing spondylitis

by Rema Panickar

Background of the safety issue

The NPRA would like to highlight the introduction of a lower recommended dose of etoricoxib for rheumatoid arthritis and ankylosing spondylitis.

This update follows analysis by the European Medicines Agency (EMA) of data from clinical trials conducted by the marketing authorisation holder on the efficacy and safety of etoricoxib 60 mg once daily for the treatment of rheumatoid arthritis and ankylosing spondylitis. EMA required the marketing authorisation holder to conduct these trials following a review of the benefits and risks of etoricoxib, during which concerns were raised on the safety of the long-term use of etoricoxib 90 mg once daily.

These trials revealed evidence that the 60 mg dose is effective in rheumatoid arthritis and ankylosing spondylitis. The 90 mg dose was shown to be more efficacious for some patients, however it is not possible to predict which patients will benefit from the higher dose. Therefore the recommended starting dose has been reduced to 60 mg once daily, with the option to increase to a maximum of 90 mg once daily if necessary.

Due to the cardiovascular and other risks of etoricoxib, the lowest effective daily dose should be used for the shortest duration required, with regular review of the need for treatment.

The prescribing information of products containing etoricoxib in Europe, Canada and Australia have been updated with this new dosing information.



Registered Products in Malaysia

There are currently eight (8) products containing etoricoxib registered in Malaysia since 2003, available as 30 mg, 60 mg, 90 mg, and 120 mg preparations.

Local ADR Reports

Since 2003, the NPRA has received 434 ADR reports with 772 adverse events suspected to be related to etoricoxib. The dosages used in these cases were mostly 90 mg and 120 mg. Majority of the adverse events involved skin disorders, such as rash, pruritus and Stevens-Johnson syndrome. Other commonly reported adverse events were oedema (facial, periorbital, or peripheral), mouth ulceration, vomiting, and acute renal failure.

Regulatory Action

The package inserts and consumer medicine information leaflets of all products containing etoricoxib are required to be updated with these new recommended doses, as stated in the Malaysian Drug Control Authority (DCA) directive dated 12 July 2017 [[Ref: \(18\) dlm.BPFK/PPP/07/25 Jilid 1](#)] which may be downloaded from the NPRA website.

Advice to Healthcare Professionals

- The revised recommended dose of etoricoxib is 60 mg once daily for patients with rheumatoid arthritis and ankylosing spondylitis.
- An increased dose of 90 mg once daily may be effective for some patients with insufficient relief from symptoms. Down-titration to 60 mg once daily may be appropriate once the patient is clinically stabilised.
- Please report any adverse reactions suspected to be related to the use of etoricoxib to the NPRA.

What's New?

Annie & Mac's Adventures: Pharmacovigilance Comic Book Pilot Survey

"Children make great teachers."

With this in mind, the Uppsala Monitoring Centre (UMC) in Sweden, which is a WHO Collaborating Centre for International Drug Monitoring, created a communication project to reach the younger generation and teach children important information on medication safety.

What better way to help children understand pharmacovigilance than through a comic book!

"Annie & Mac's Adventures" is aimed at children aged 9-13 years, and contains exciting stories as well as activity pages to engage young minds.

The UMC initiated a pilot phase of the comic's first issue in various countries, including Malaysia. The NPRA conducted this pilot survey involving a group of primary school children in Kuala Lumpur.



It was delightful to watch the children excitedly flip through the comic book, captivated by the action-packed stories and eager to complete all the activity pages.

The key messages were well understood. After reading through the comic, the children were able to explain the dangers of counterfeit medicines available on the market, what side effects are, and how side effects occur in the body. The children also had many interesting ideas on new characters and storylines. The feedback was provided to the UMC for use in future issues of the comic.

We look forward to further distribution of this comic book once the worldwide pilot test has been completed. By giving children information on medication safety, we hope they will play a part in influencing and educating the wider community.



What's New?

Pharmacovigilance Inspection Training at the UK MHRA



In May 2017, two NPRA officers were sent to London, as observers of a pharmacovigilance (PV) inspection organised by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA).

Previously, in August and November 2016, NPRA officers were briefed on PV inspection by an Expert Inspector from the MHRA and officers from the Vigilance & Risk Management of Medicines (VRMM) team. Topics covered included an introduction to PV inspection, PV inspection legislation and structure, as well as Good Pharmacovigilance Practice (GPvP) [please refer to *MADRAC Bulletin December 2016*].

This latest hands-on training attachment in London aimed to provide exposure to the processes involved in the preparation, opening, conduct and closing of a PV inspection at a local pharmaceutical company in the UK, as well as allow application of the signal detection methods mentioned by the VRMM.

Apart from establishing new connections within the MHRA, the NPRA officers have also gained new insights and a first-hand experience to establish PV inspection back home in Malaysia.

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, as well as traditional products and health supplements.


To report an adverse drug reaction:


1. Visit npra.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 hard copy forms may be submitted via email, post or fax to:

 The Pharmacovigilance Section,
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