Drug News
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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in March 2022 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

Canada: Summary Safety Review: Oral, over-the-counter diphenhydramine-containing products - Assessing the potential risk of serious side effects in children

On 1 March 2022, Health Canada announced that it assessed the potential risk of serious side effects in children of oral, over-the-counter (OTC) diphenhydramine-containing products (DCPs).

Most DCPs are authorized for sale in Canada as OTC drugs to relieve symptoms of several medical conditions, including allergies. They belong to a group of drug products known as first-generation antihistamines.

In 2019, the Canadian Society of Allergy and Clinical Immunology (CSACI) published a position statement recommending the use of newer-generation antihistamines for the treatment of hay fever (allergic rhinitis) and hives (urticaria) because of the side effects associated with first-generation antihistamines. The statement did not identify new safety information for first-generation antihistamines, however, it generated interest from the Canadian public about the safety of DCPs at recommended or higher doses, specifically in children.

Diphenhydramine has the potential for problematic use and overdose that can lead to serious side effects in children, including seeing and hearings things that are not there (hallucinations), sudden change in the brain's normal electrical activity (seizures), palpitations, difficulty in breathing and coma. The use of DCPs to treat allergic symptoms is widespread, particularly in children. As a precaution, Health Canada assessed known and potential serious side effects associated with the use of DCPs in children under 2 years of age, and serious side effects related to problematic use and accidental overdose in children under 18 years of age. The purpose of the review was to determine if there was a change in the type and/or frequency of side effects associated with the use of DCPs in these vulnerable populations.

Health Canada reviewed the available information from searches of the Canada Vigilance database, published literature, and the manufacturer. Health Canada reviewed 52 Canadian case reports involving diphenhydramine use in children, received between December 1983 and March 2019; none were fatal. Of the 52 cases, only 5 contained enough information to determine whether there was a link between the use of diphenhydramine and the reported serious side effects in children:

- One case involved a child under 2 years of age with difficulty in controlling movements (dyskinesia); this case was found to be probably linked with the use of oral diphenhydramine at the recommended dose.
- Four cases involved problematic use or overdose in children. Reported side effects included false beliefs (delusions), hallucinations, disorientation, dizziness, hyperactivity, widened (dilated) pupils, rapid heart rate (tachycardia), and seizure, alone or accompanied by vomiting. Two cases were found to be probably linked, and 2 were found to be possibly linked with the use of oral diphenhydramine.

Health Canada also reviewed international literature cases. The side effects reported in these cases were consistent with the known safety profile of diphenhydramine.

Health Canada's review of the available information found no change in the type or frequency of serious side effects associated with the use of DCPs to warrant regulatory action at this time.

In Hong Kong, there are 61 registered pharmaceutical products containing diphenhydramine which are in oral dosage forms. All products are pharmacy only medicines. As of the end of March 2022, the Department of Health (DH) had received one case of adverse drug reaction related to diphenhydramine, but this case was not related to drug use in children. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

European Union: Dexmedetomidine - increased risk of mortality in intensive care unit patients aged 65 years and less

On 11 March 2022, European Medicines Agency (EMA) announced that its Pharmacovigilance Risk Assessment Committee (PRAC) discussed a direct healthcare professional communication (DHPC) containing important safety information for dexmedetomidine.

This DHPC aims to inform healthcare professionals of the increased risk of mortality when administering dexmedetomidine in intensive care unit (ICU) patients aged 65 years and less, compared with alternative sedatives.

SPICE III study was a randomised clinical trial comparing the effect of sedation with dexmedetomidine on all-cause mortality (deaths from any cause) with the effect of usual standard of care in 3,904 critically ill adult ICU patients in need of mechanical ventilation. The study showed no difference in the overall 90-day mortality between dexmedetomidine and alternative sedatives (propofol, midazolam). However, dexmedetomidine was associated with an increased risk of mortality in patients aged 65 years and less, compared with alternative sedatives.

The product information for dexmedetomidine is being updated with a warning describing the evidence and risk factors. Healthcare professionals are being advised to weigh these findings against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in this age group.

The DHPC for dexmedetomidine will be forwarded to EMA's Committee for Medicinal Products for Human Use (CHMP). Following the CHMP decision, the DHPC will be disseminated to healthcare professionals by the marketing authorisation holder, according to an agreed communication plan, and published on the Direct healthcare professional communications page and in national registers in European Union Member States.

In Hong Kong, there are 6 registered pharmaceutical products containing dexmedetomidine. All products are prescription-only medicines. As of the end of March 2022, the Department of Health (DH) had received one case of adverse drug reaction related to dexmedetomidine. The DH will remain vigilant on any safety updates issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

The United Kingdom: Cladribine (Mavenclad) - New advice to minimise risk of serious liver injury

On 15 March 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that liver monitoring requirements for cladribine in the treatment of multiple sclerosis have been introduced following uncommon cases of serious liver injury.

A recent European review of safety data has identified 16 cases of liver injury post-marketing, including serious cases requiring discontinuation and one fatal case of hepatic failure in a patient with alcohol-related liver disease and who was undergoing tuberculosis treatment with isoniazid. Within the cases of liver injury reviewed, there were rare reports of jaundice and serum transaminase levels greater than 1000 IU/L. However, the majority of cases had mild clinical symptoms.

A small number of cases of liver injury have also been seen in clinical trials. In some of these cases, patients developed significantly increased serum transaminase levels related to treatment. These serious events resolved within 4 months after cladribine was discontinued (in the cases reporting a final outcome). Alternative causes were excluded in one patient, and none required a liver biopsy. Data from clinical trials did not suggest a dose-dependent effect.

Time to onset of liver injury varied, with most cases occurring within 8 weeks after start of the first treatment course. Some patients had underlying hepatic disorders or a history of hepatic injury related to other medicines. A causal

mechanism has not been identified.

The product information and the educational materials will be revised to include updated advice for healthcare professionals and patients on the risk of serious liver injury. Liver injury will be included as an adverse drug reaction of uncommon frequency (may affect up to 1 in 100 patients).

In the United Kingdom, up to 25 January 2022, MHRA has received 2 reports of hepatic injury in patients receiving cladribine for multiple sclerosis via the Yellow Card scheme. Both patients developed liver injury within a month of starting cladribine treatment and in one case the alanine aminotransferase (ALT) level exceeded 1000 IU/L.

Cladribine is also available in other medicines. Leustat injection and Litak 2mg/ml solution for injection are authorised to treat patients with hairy cell leukaemia and Leustat injection is also approved for the treatment of B-cell chronic lymphocytic leukaemia. Prescribers of these medicines should continue to follow the current recommendations on patient monitoring.

Advice for healthcare professionals:

- A small number of cases of clinically significant liver injury have been reported during cladribine treatment for multiple sclerosis.
- Most events occurred within 8 weeks of the start of the first treatment course of cladribine.
- Before starting cladribine check if there is a history of liver disorders, including hepatic injury related to other medicines.
- Monitor liver function tests (including total bilirubin) before each treatment course in years 1 and 2; and, if clinically necessary, during treatment.
- Urgently check liver function tests (including bilirubin) in patients with symptoms or signs of liver injury.
- Discontinue or interrupt cladribine treatment in patients with hepatic dysfunction or unexplained increases in liver enzymes.

In Hong Kong, there is one registered pharmaceutical product containing cladribine, namely Mavenclad Tablets 10mg (HK-65910). The product is registered by Merck Pharmaceutical (HK) Limited. It is a prescription-only medicine. As of the end of March 2022, the Department of Health (DH) had not received any case of adverse drug reaction related to cladribine. Related news was previously issued by European Medicines Agency and Singapore Health Sciences Authority, and was reported in Drug News Issues No. 147 and 148 respectively. The DH issued letters to inform local healthcare professionals to draw their attention on 15 January 2022. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Metformin in pregnancy - Study shows no safety concerns

On 15 March 2022, Medicines and Healthcare products Regulatory Agency (MHRA) announced that a large study has shown no safety issues of concern relating to the use of metformin during pregnancy.

Uncontrolled hyperglycaemia in the time around conception (periconceptional phase) and during pregnancy is associated with increased risks to the baby and the patient. Good blood glucose control reduces the risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. National guidelines in the United Kingdom already recommend metformin for use in diabetes during pregnancy and gestational diabetes if a healthcare professional feels it is appropriate.

Following a European review of data from a non-interventional cohort study of population registries in Finland (the CLUE study), the product information for metformin is being updated to permit the use of metformin during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed. The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines has also reviewed the data from the study and agreed that the product information should be updated.

The study investigated immediate and longer-term effects of exposure to metformin in-utero on children born to patients with pre-existing type 2 diabetes, gestational diabetes, or polycystic ovary syndrome. The results of the study were reassuring, with no safety signals of concern identified for use of metformin in pregnancy relating either to those who were pregnant or their baby. Among secondary outcomes, similar rates of births that were small (low weight) for gestational age were observed with exposure to metformin and within the group of patients with untreated gestational

diabetes. By contrast, an increased risk of small for gestational age was observed with exposure to metformin compared with insulin, which may relate to an overall increase in body weight due to use of insulin.

The advice in the Summary of Product Characteristics for metformin products is being updated. Corresponding changes are also being made to the Patient Information Leaflet. These changes have already been made to the brand-leader Glucophage. Some fixed-dose combination products containing metformin contain other active substances that should be avoided during pregnancy. The product information for fixed-dose combination products containing metformin will be reviewed and advice on use in pregnancy updated if appropriate.

This update to the product information reflects clinical practice and advice in current United Kingdom guidelines.

In Hong Kong, there are 118 registered pharmaceutical products containing metformin. All products are prescription-only medicines. As of the end of March 2022, the Department of Health (DH) had received 19 cases of adverse drug reaction related to metformin, but these cases were not related to low birth weight. The DH will remain vigilant on any safety update of the drug issued by other overseas drug regulatory authorities.

The United States: FDA recommends thyroid monitoring in babies and young children who receive injections of iodine-containing contrast media for medical imaging

On 30 March 2022, US Food and Drug Administration (FDA) announced that newborns and children through 3 years old are recommended to have follow-up thyroid monitoring within 3 weeks after receiving injections of contrast media containing iodine for X-rays and other medical imaging procedures, based on its recent review of published studies. FDA's review showed that underactive thyroid or a temporary decrease in thyroid hormone levels were uncommon. However, the conditions should be identified and treated early when needed to prevent potential future complications. Newborns, particularly those born premature, and children in their first 3 years with underlying conditions such as heart issues may be at higher risk for problems of the thyroid.

FDA has approved a new warning to the prescribing information for the entire class of iodinated contrast media (ICM) injections and monitoring recommendations for children 3 years or younger. The warning describes the risk of underactive thyroid or a temporary decrease in thyroid hormone levels. These risks and recommendations pertain to ICM given as an injection through an artery or vein.

Since 2015 when FDA first alerted the public about cases of underactive thyroid in infants receiving ICM, six new research studies evaluating this risk have been published. FDA reviewed these six studies and the five earlier ones published in the medical literature that assessed thyroid function in a range of 10 to 2,320 children from birth through 3 years who were exposed to ICM. Most cases of decreased thyroid hormone levels were temporary and did not require treatment. The reported rate ranged from 1 percent to 15 percent and tended to be higher in newborns, particularly those who were preterm. Patients with cardiac conditions were at greatest risk since they often require high doses of contrast during invasive cardiac procedures such as catheterization and computed tomography. The time from ICM exposure to diagnosis ranged between 8.5 and 138 days, with most occurring within 3 weeks in some of the publications.

In 2015, FDA required the manufacturers of ICM products to conduct a study to investigate this safety issue further. However, FDA has concluded based on its review of the published studies that there is compelling evidence of a significant risk for underactive thyroid or a temporary decrease in thyroid hormone levels in newborns and children through 3 years after exposure to ICM. Therefore, the study by the manufacturers is no longer needed.

Healthcare professionals should perform appropriate monitoring of patients from birth through 3 years for the possibility of hypothyroidism or a temporary decrease in thyroid hormone levels following exposure to ICM. Consider evaluating thyroid function within 3 weeks, especially in term and preterm neonates and children with some underlying conditions. If thyroid dysfunction is detected, treat and monitor thyroid function as clinically needed to avoid future cognitive and other developmental disabilities. Certain pediatric patients are at an increased risk, including those who are newborns or have very low birth weight, prematurity, or the presence of cardiac or other conditions such as those requiring

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care in neonatal or pediatric intensive care units. Patients with cardiac conditions may be at greatest risk since they often require high doses of contrast during invasive cardiac procedures.

In Hong Kong, there are registered pharmaceutical products which are iodine-containing contrast agents containing iodixanol (2 products), iohexol (2 products), iopamidol (2 products), iopromide (2 products), ioversol (4 products), iomeprol (4 products), iobitridol (6 products) and iodised oil (1 product). All products are prescription-only medicines. As of the end of March 2022, the Department of Health (DH) had received adverse drug reaction related to iodixanol (3 cases), iohexol (1 case), iopamidol (3 cases), iopromide (7 cases), iobitridol (4 cases) and iodised oil (2 cases), but these cases were not related to decreased thyroid function. The DH has not received any case of adverse drug reaction related to ioversol and iomeprol.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in Drug News Issue No. 73. The DH issued letters to inform local healthcare professionals to draw their attention on 18 November 2015. In April 2016, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and decided that the sales pack labels and/or package inserts of iodine-containing contrast agents should include safety warnings on the risk of hypothyroidism. In light of the above FDA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 31 March 2022, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Drug Recall

Recall of 4 batches of "Orphenadrine Citrate 100mg Extended Release Tablets"

On 24 March 2022, the Department of Health (DH) endorsed a licensed drug wholesaler, Sino-Asia Pharmaceutical Supplies Limited (Sina-Asia), to recall four batches (batch number: JX6411, KC3303, KE4348 and LA7703) of Orphenadrine Citrate 100mg Extended Release Tablets from the market due to the presence of an impurity in the product.

The DH received notification from Sino-Asia on 24 March 2022 stating that the overseas manufacturer informed them the above batches of concerned product contains a nitrosamine impurity, namely N-methyl-N-nitroso-2-[(2 methylphenyl) phenylmethoxy] ethanamine, exceeding the accepted level. As a precautionary measure, Sino-Asia is voluntarily recalling the above batches from the market.

The above product contains the active ingredient orphenadrine citrate and is a prescription medicine used for treatment of muscle spasms. The product was unregistered but imported for the treatment of particular patients by the Hospital Authority.

As of the end of March 2022, the DH has not received any adverse reaction reports in connection with the above batches of product. A notice was posted in the Drug Office website on 24 March 2022 to alert the public of the product recall. The DH will closely monitor the recall.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $50,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.

Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

Useful Contact

Drug Complaint:

Tel: 2572 2068
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Adverse Drug Reaction (ADR) Reporting:

Tel: 2319 2920
Fax: 2319 6319
E-mail: adr@dh.gov.hk
Link: http://www.drugoffice.gov.hk/adr.html

Post: Adverse Drug Reaction and Adverse Event Following Immunization Unit,
Drug Office, Department of Health,
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