Drug News
藥 物 情 報

Issue Number 164

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in June 2023 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

Australia: Oral anticoagulants can cause serious kidney damage in rare circumstances

On 1 June 2023, the Therapeutic Goods Administration (TGA) announced that a warning about anticoagulant-related nephropathy (ARN) had been added to the Product Information (PI) for all oral anticoagulants. There are 4 oral anticoagulants available in Australia: apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto) and warfarin (Coumadin, Marevan).

This is a rare but serious adverse event resulting from profuse glomerular bleeding. It has the potential to cause irreversible kidney damage and death. Although rare, ARN is likely to be underdiagnosed as a cause of acute kidney injury. Early detection and intervention of ARN is critical to minimising its associated morbidity and mortality. Therefore, awareness of this adverse event among health professionals is important.

There have been reports of ARN in patients taking oral anticoagulants, mainly from overseas. TGA investigated this safety signal. TGA also sought expert advice from the Advisory Committee on Medicines (ACM) about mitigating the risk of harm in Australia. The ACM noted this adverse event is now well documented in the medical literature with warfarin and there is growing evidence for other oral anticoagulants. The ACM supported a class-wide warning being added to the PI for all oral anticoagulants. This is because these medicines are widely used, and this adverse event is serious. The ACM highlighted that ARN is a rare, but serious event that is likely underdiagnosed and requires prescriber education around its presentation (as acute kidney injury) and management. Additionally, the ACM advised that the term 'anticoagulant-related nephropathy' should be included in the PI as an adverse event, distinct from 'haematuria or genitourinary haemorrhage' and 'acute kidney injury'.

The ACM do not consider a warning for parenteral anticoagulants is needed at this stage. This is because they are mainly used in hospitals and for a shorter duration.

It is important that health professionals are aware of this side effect, as early detection and treatment is critical to reducing permanent kidney damage and death. Although ARN is rare, it is likely underdiagnosed. This is because kidney biopsy is required for a definitive diagnosis but is rarely performed in people taking anticoagulants. Also, many patients who develop ARN have comorbidities that may explain their acute kidney injury presentation.

If health professionals are treating patients taking oral anticoagulants, talk to them about the risk of ARN. Close monitoring, including renal testing, is recommended for those with excessive anticoagulation (or supratherapeutic INR for those on warfarin) and haematuria. Monitoring is also recommended for patients with compromised renal function who are taking apixaban, dabigatran or rivaroxaban. Be aware that ARN has been reported in patients who do not have pre-existing kidney disease.

As of 24 April 2023, one case of ARN had been reported to the TGA, where the sole suspect was warfarin. The patient was taking concomitant amoxicillin. The case describes resolution of the adverse event one month after warfarin was stopped.

In Hong Kong, there are registered pharmaceutical products which are oral anticoagulants containing apixaban (4 products), dabigatran (3 products),

edoxaban (3 products), rivaroxaban (11 products) and warfarin (4 products). All products are prescription-only medicines.

As of the end of June 2023, the Department of Health (DH) had received adverse drug reaction related to apixaban (61 cases; of which one case was related to kidney disorder and one case was related to renal function abnormal), dabigatran (20 cases; of which one case was related to acute kidney injury with haematuria), edoxaban (29 cases), rivaroxaban (26 cases) and warfarin (14 cases). For edoxaban, rivaroxaban and warfarin, the adverse drug reactions received were not related to kidney damage. In light of the above TGA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 2 June 2023, and the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board .

Singapore: Withdrawal of Pholcodine-Containing Medicines in Singapore

On 22 June 2023, the Health Sciences Authority (HSA) announced it would like to inform the public that all pholcodine-containing medicines will be withdrawn in Singapore. The company marketing these products, iNova Pharmaceuticals (Singapore) Pte Ltd, is cancelling the registrations of these pholcodine-containing medicines and ceasing their supply in the local market. This is a precautionary measure due to overseas findings of a rare and very small risk of severe allergic reactions (i.e., anaphylaxis) to muscle relaxants (neuromuscular blocking agents or NMBAs) used during general anaesthesia in patients who have taken pholcodine, particularly in the preceding 12 months.

A safety study (ALPHO study) conducted in France found that there is a link between pholcodine and an increased risk of anaphylaxis with NMBAs used during general anaesthesia in surgeries. This safety risk is rare and assessed to be very low. To date, HSA has not received any local reports of NMBA-related anaphylactic reactions suspected to be associated with pholcodine.

HSA has conducted a review of the study and other available safety data and considered whether there are effective measures that can be taken to mitigate this safety risk. In consultation with medical experts from its Product Vigilance Advisory Committee, HSA has concluded that the potential risks outweigh the benefits of these products, and pholcodine-containing medicines should be withdrawn from the local market as a precautionary measure.

Patients are advised:

- If they are undergoing surgery involving the use of general anaesthesia and had taken any pholcodine-containing medicines, particularly in the past 12 months, they should inform the anaesthetist or doctor. The risk of anaphylaxis during surgeries is very rare. Anaesthetists are well trained to manage anaphylaxis and will take this into consideration during the surgery.
- To consult the doctor or pharmacist if they have any questions or concerns on the pholcodine-containing medicines or for advice on alternative treatments for dry cough.

In view of its regulatory decision, HSA has issued letters to healthcare professionals on the matters related to the withdrawal of pholcodine-containing products.

In Hong Kong, there are 27 registered pharmaceutical products containing pholcodine. All products are pharmacy only medicines. As of the end of June 2023, the Department of Health (DH) had received one case of adverse drug reaction related to pholcodine, but this case was not related to anaphylaxis. Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News since Issue No. 17, with the latest update reported in Drug News Issue No. 161. The DH issued letters to inform local healthcare professionals to draw their attention on 1 March 2023. On 6 July 2023, the Registration Committee of the Pharmacy and Poisons Board reviewed the safety of pholcodine-containing medicines and decided to, in the public interest as stipulated by the Pharmacy and Poisons Regulations (Cap. 138A), deregister pharmaceutical products containing pholcodine with effect from January 1, 2024, after taking into consideration various factors including the latest recommendations on pholcodine by overseas regulatory authorities, and advice given by local experts.

The United Kingdom: Calcium chloride, calcium gluconate: potential risk of underdosing with calcium gluconate in severe hyperkalaemia

On 27 June 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced

an alert for the potential risk of underdosing with calcium gluconate in severe hyperkalaemia. Calcium salts (either calcium chloride or calcium gluconate) are used to stabilise the myocardium and prevent cardiac arrest in patients experiencing severe hyperkalaemia. However, the two salts are not equivalent in terms of calcium dose. Ensure the correct dose is administered to avoid underdosing of calcium. If treated sub-optimally, hyperkalaemia can be fatal.

Treatment of severe hyperkalaemia (plasma concentration ≥6.5 mmol/l) is a medical emergency and treatment must not be delayed. Calcium gluconate is used to stabilise the myocardium and prevent arrythmias and cardiac arrest.

Calcium salts have previously been used off-label for the treatment of myocardial excitability in severe hyperkalaemia, but the MHRA recently authorised the use of calcium gluconate in acute severe hyperkalaemia and in cardiac resuscitation due to severe hyperkalaemia. Calcium gluconate therapy should be started only in cases of documented severe hyperkalaemia. It should not be routinely administered during cardiac arrest.

In the United Kingdom (UK), updated Clinical Practice Guidelines in the Treatment of Acute Hyperkalaemia in Adults were published in 2020. Calcium salts do not reduce the serum potassium but are given to protect the heart. The guideline recommends use of either calcium chloride or calcium gluconate. However, the salts are not equivalent in terms of calcium dose. To achieve the recommended calcium dose of 6.8 mmol, 30ml of calcium gluconate 10% or 10ml calcium chloride 10% must be used. Both calcium gluconate and calcium chloride preparations are available in 10ml vials at 10% (w/v) concentration, therefore 3 vials of calcium gluconate are required to reach the appropriate dose but only 1 vial of calcium chloride. The method of administration should be by slow intravenous injection, which may need to be repeated.

Electrocardiogram (ECG) changes may provide evidence of potassium toxicity but are not always present initially. ECG monitoring is advised for potassium levels above 6.0 mmol/L. Calcium gluconate should show an effect on ECG abnormalities within 3 minutes of administration and its action is expected to last for 30 to 60 minutes. A 30ml bolus dose of calcium gluconate 10% should be given by intravenous injection over 10 minutes. The effect of calcium salts is temporary so consider a repeat dose if ECG abnormalities remain within 5 to 10 minutes after the initial dose is complete.

Calcium salts do not lower potassium levels. The risk of arrythmias and cardiac arrest increases in proportion to severity of hyperkalaemia. Measures to lower potassium levels and to address underlying causes of hyperkalaemia must be taken immediately.

Tissue necrosis is a serious adverse event if extravasation occurs during administration of both intravenous (IV) calcium salts. Ensure reliable intravenous access and test with flush prior to administration.

Review of underdosing of calcium gluconate:
The MHRA has reviewed available UK data related to inappropriate use of calcium gluconate and identified isolated cases where medication errors have occurred, including one death, where 10ml of calcium gluconate was used during cardiopulmonary resuscitation (Yellow Card literature report). Reports from the National Reporting Learning System received since the guideline was updated indicate that 6 incidents showed incorrect calcium gluconate administration and monitoring in the context of severe hyperkalaemia and cardiac arrest (5 fatal, 1 unknown outcome). The safety concerns in these incidents related to calcium gluconate underdosing; lack of repeat dosing where indicated; lack of potassium-lowering treatment and lack of or inappropriate ECG monitoring.

Following a review by the MHRA and advice from the Commission on Human Medicines, the product information for these medicines will be updated to more clearly define the safe and effective administration of calcium gluconate for severe hyperkalaemia and to warn of the potential for underdosing.

The MHRA recently authorised use of calcium gluconate for the treatment of myocardial excitability in severe hyperkalaemia, which was previously off-label. Healthcare professionals are reminded that calcium gluconate is not usually recommended for the treatment of cardiac arrest except for where there is concomitant severe hyperkalaemia. Bolus injection is recommended in these circumstances.

Healthcare professionals are advised:

- calcium salts (either calcium chloride or calcium gluconate) are used to stabilise the myocardium and prevent cardiac arrest – these two products are not dose-equivalent
- be alert to the risk of inadvertent underdosing if calcium gluconate is used instead of calcium chloride and verify the calcium salt details before administration: 30ml of calcium gluconate 10% provides 6.8mmol of calcium (equivalent to 10ml of calcium chloride 10%)
- administration must be by slow intravenous injection of the whole dose over 10 minutes
- repeat doses may be required as the effect of calcium is temporary, lasting 30 to 60 minutes

In Hong Kong, there are four registered pharmaceutical products containing calcium gluconate as the single active ingredient for injection, namely Calcium Gluconate Kabi Solution for Injection/Infusion 1000mg/10ml (HK-66892), 10% Calcium Gluconate Inj (B Braun) (HK-37887), Calcium-Aguettant Solution for Injection/Infusion 10% w/v (HK-66062) and Calcium Gluconate-Hameln Solution for Injection 10% w/v (HK-66660); and there are three registered pharmaceutical products containing calcium chloride as the single active ingredient, namely Calcium Chloride Injection BP 10% w/v 1g/10mL (HK-66744), Calcium Chloride Demo Solution for Infusion 10% w/v 1g/10mL (HK-67621) and Calcium Chloride Injection USP 1000mg/10mL (HK-63078). They are all prescription-only medicines.

Amongst the abovementioned products, only Calcium Gluconate Kabi Solution for Injection/Infusion 1000mg/10ml (HK-66892), Calcium Chloride Injection BP 10% w/v 1g/10mL (HK-66744) and Calcium Chloride Demo Solution for Infusion 10% w/v 1g/10mL (HK-67621) are approved in Hong Kong for hyperkalaemia; and their package inserts have already included a warning for use with caution in patients with cardiac disease.

As of the end of June 2023, the Department of Health (DH) had not received any adverse drug reaction (ADR) cases related to calcium gluconate injection or calcium chloride injection. In light of the above MHRA's announcement, the DH issued letters to inform local healthcare professionals to draw their attention on 28 June 2023. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

The United Kingdom: Non-steroidal anti-inflammatory drugs (NSAIDs): potential risks following prolonged use after 20 weeks of pregnancy

On 27 June 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) announced a reminder to healthcare professionals that use of systemic (oral and injectable) NSAIDs such as ibuprofen, naproxen, and diclofenac is contraindicated in the last trimester of pregnancy (after 28 weeks of pregnancy).

A review of data from a 2022 study has identified that prolonged use of NSAIDs from week 20 of pregnancy onwards may be associated with an increased risk of oligohydramnios (low levels of amniotic fluid surrounding the baby) and fetal renal dysfunction. Some cases of constriction of the ductus arteriosus (narrowing of a connecting blood vessel in the baby's heart) have also been identified at this early stage.

If, following consultation between the patient and a healthcare professional, use of a systemic NSAID after week 20 of pregnancy is considered necessary, it should be prescribed for the lowest dose for the shortest time and additional neonatal monitoring considered if used for longer than several days. This is in addition to giving advice to discontinue use of any NSAID in the last trimester of pregnancy.

Healthcare professionals are advised:

- systemic (oral and injectable) NSAIDs are contraindicated during the last trimester (after 28 weeks) of pregnancy due to the risk of premature closure of the ductus arteriosus and renal dysfunction in the fetus and due to prolongation of maternal bleeding time and inhibition of uterine contractions during labour;
- a review of data from a 2022 study has identified that prolonged use of NSAIDs from week 20 of pregnancy onwards may be associated with an increased risk of:
  (a) oligohydramnios resulting from fetal renal dysfunction; this may occur shortly after initiation, although it is usually reversible upon discontinuation; and
  (b) cases of constriction of the ductus arteriosus, most of which resolved after treatment cessation;
- avoid prescribing systemic NSAIDs from week 20 of pregnancy unless clinically

Safety Update

required and prescribe the lowest dose for the shortest time in these circumstances;

- antenatal monitoring for oligohydramnios should be considered if the mother has been exposed to NSAIDs for several days after week 20 of pregnancy; the NSAID should be discontinued if oligohydramnios is found or if the NSAID is no longer considered to be clinically necessary
- to instruct patients who are pregnant to avoid use of NSAIDs available without prescription from week 20 of pregnancy onwards unless advised by their healthcare professional

In Hong Kong, there are registered pharmaceutical products containing non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and diclofenac. As of the end of June 2023, the Department of Health (DH) had received adverse drug reaction related to ibuprofen (4 cases), naproxen (3 cases) and diclofenac (19 cases), but these cases are not related to oligohydramnios, fetal renal dysfunction or constriction of the ductus arteriosus.

Related news was previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 132. The DH issued letters to inform local healthcare professionals to draw their attention on 16 October 2020. In February 2022, the Registration Committee of the Pharmacy and Poisons Board (the Committee) discussed the matter on the warnings related to the risk of oligohydramnios, fetal renal dysfunction and constriction of the ductus arteriosus when used in pregnancy; and decided that the sales pack or package insert of the above products should include the relevant safety information. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

Drug Incident

Man arrested for illegal sale and possession of unregistered pharmaceutical products, Part 1 poisons and antibiotics

On 21 June 2023, the Department of Health (DH) conducted an operation against the suspected illegal sale and possession of unregistered pharmaceutical products, Part 1 poisons and antibiotics. A 45-year-old man was arrested during the operation.

Upon intelligence, a shop in Cheung Sha Wan was found selling various unregistered pharmaceutical products, including pain killers, cough and cold medicines, anti-dizziness and antiemetic drugs, as well as external preparations. All the products did not bear Hong Kong registration numbers for pharmaceutical products, while most of them are labelled in foreign languages (including Japanese, Korean and English).

A preliminary investigation indicated that, among the relevant medicines seized during the enforcement operation, 13 types of products contain Part 1 poisons under the Pharmacy and Poisons Ordinance (Cap. 138) (including ibuprofen, dihydrocodeine, methylephedrine, fluocinolone, triamcinolone acetonide, hydrocortisone, difluprednate, diclofenac, felbinac and hyoscine) and/or antibiotic substances under the Antibiotics Ordinance (Cap. 137) (including bacitracin and neomycin). A 45-year-old man was arrested by the Police for illegal sale and possession of unregistered pharmaceutical products, Part 1 poisons and antibiotics. The DH's investigation is ongoing.

Ibuprofen is a non-steroidal anti-inflammatory pain killer and its side effects include nausea, gastrointestinal discomfort and peptic ulcers. Dihydrocodeine is an opioid analgesic and may cause nausea, vomiting and constipation. Side effects of methylephedrine include tachycardia, anxiety, restlessness and insomnia. Fluocinolone, triamcinolone acetonide, hydrocortisone and difluprednate are steroid substances for treating inflammation. Inappropriate application of steroids could cause skin problems and systemic side effects such as moon face, high blood pressure, high blood sugar, adrenal insufficiency and osteoporosis. Diclofenac and felbinac are non-steroidal anti-inflammatory drugs which could be used topically to relieve pain. Inappropriate use of diclofenac and felbinac may cause erythema and dermatitis. Common side effects of hyoscine include dry mouth, blurred vision and constipation. Inappropriate or excessive use of antibiotics can lead to antibiotic resistance.

Products containing the above ingredients should only be supplied by a pharmacy under the supervision of a registered pharmacist, among which those containing fluocinolone, triamcinolone

acetonide, difluprednate, bacitracin or neomycin also require a doctor's prescription.

Members of the public should not self-medicate without advice from healthcare professionals. People who have purchased and used the above products should stop using them and consult healthcare professionals if they are in doubt or feeling unwell after use. A press release was posted in the Drug Office website on 21 June 2023 to alert the public of the drug incident.

DH investigates suspected illegal possession and sale of unregistered pharmaceutical products

On 29 June 2023, the Department of Health (DH) conducted an operation against a pharmacy in Tseung Kwan O for suspected illegal possession and sale of unregistered pharmaceutical products.

Upon intelligence, a pharmacy in Tseung Kwan O was found displaying for sale various unregistered pharmaceutical products, including two eye drops and an external preparation. All the products do not bear Hong Kong registration numbers for pharmaceutical products in the package, while most of them are labelled in foreign languages (including Japanese and English).

Preliminary investigation indicated that, among the relevant medicines seized during the enforcement operation, two products contain neostigmine, which is a Part 1 poison under the Pharmacy and Poisons Ordinance (Cap. 138). The investigation is ongoing.

Eye drops with neostigmine can be used in the management of glaucoma. It may cause ocular pain and irritation as well as blurred vision as side effects. Products containing the above ingredient should only be supplied by a pharmacy under the supervision of a registered pharmacist and under a doctor's prescription.

Members of the public should not self-medicate without advice from healthcare professionals. People who have purchased and used the above products should stop using them and consult healthcare professionals if in doubt or feeling unwell after use. A press release was posted in the Drug Office website on 29 June 2023 to alert the public of the drug incident.

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.

All registered pharmaceutical products should carry a Hong Kong registration number on the package in the format of "HK-XXXXX". The products mentioned in the above incidents were not registered pharmaceutical products under the Ordinance in Hong Kong. Their safety, quality and efficacy cannot be guaranteed. Members of the public were exhorted not to use products of unknown or doubtful composition. They should stop using the aforementioned products immediately if they had them in their possession and to consult healthcare professionals if they felt unwell after taking the products. The products should be destroyed or disposed properly, or submitted to the Department's Drug Office during office hours.

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/

Useful Contact

Drug Complaint:

Tel: 2572 2068

Fax: 3904 1224

E-mail: pharmgeneral@dh.gov.hk

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,
Room 1856, 18/F, Wu Chung House,
213 Queen's Road East,
Wanchai, Hong Kong

The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.