Drug News
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Issue Number 49

This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in November 2013 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

US: Recommendations to decrease risk of spinal column bleeding and paralysis of low molecular weight heparins

On 6 November 2013, the Food and Drug Administration (FDA) of the US recommended healthcare professionals to consider carefully the timing of spinal catheter placement and removal in patients taking low molecular weight heparins, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal. These new timing recommendations can decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. The US labels of all low molecular weight heparins, including generic enoxaparin products and similar products, will be updated accordingly.

Healthcare professionals involved in performing spinal/epidural anesthesia or spinal punctures should determine, as part of a preprocedure checklist, whether a patient is receiving anticoagulants and identify the appropriate timing of enoxaparin dosing in relation to catheter placement or removal. To reduce the potential risk of bleeding, both the dose and the elimination half-life of the anticoagulant should be considered:

- For enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of deep vein thrombosis. Longer delays (24 hours) are appropriate to consider for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily).

- A postprocedure dose of enoxaparin should usually be given no sooner than 4 hours after catheter removal.

- In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

In Hong Kong, there are 16 registered pharmaceutical products belonging to low molecular weight heparins, which are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule and include the ingredients bemiparin, enoxaparin, nadroparin, reviparin and tinzaparin. All of the products are prescription only medicines indicated for prophylaxis of venous thromboembolic disease and treatment of deep vein thrombosis, unstable angina or myocardial infarction. In view of FDA's latest recommendations, a letter to healthcare professionals was issued on 7 November 2013, and the matter will be discussed in the meeting of the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee (the Registration Committee) of the Pharmacy and Poisons Board.

EU: Suspension of diacerein-containing medicines across the EU

On 8 November 2013, the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) recommended the suspension of diacerein-containing medicines across the EU. This follows a review which concluded that the benefits of diacerein, used to

treat symptoms of osteoarthritis and other degenerative joint diseases, did not outweigh its risks, particularly the risk of severe diarrhoea and potentially harmful effects on the liver.

The PRAC considered that the available data showed the benefits of diacerein to be limited. With regard to risks, although diacerein is known to cause diarrhoea as a side effect, the PRAC concluded that there was a high number of cases, particularly of severe diarrhoea, which sometimes led to complications. The PRAC was also concerned about liver problems that had been reported in some patients taking the medicine. The PRAC therefore recommended that diacerein-containing medicines be suspended in the EU until convincing evidence of a positive benefit-risk balance in a specific patient population is provided.

In Hong Kong, there is one registered pharmaceutical product containing diacerein, namely Artrodar Cap 50mg (HK-56190). It is registered by TRB Chemedica Hong Kong Limited (TRB Chemedica) and is a prescription only medicine indicated for improving the pain and function in patients with osteoarthritis. In view of EMA's recommendation, a letter to healthcare professionals was issued on 9 November 2013. The Department of Health (DH) had not received any adverse reaction report related to diacerein so far. The matter was discussed in the meeting of the Registration Committee in December 2013. The Registration Committee considered that TRB Chemedica would request the EMA for re-examination of the recommendation and decided that DH should remain vigilant on any safety updates of diacerein by other health authorities and also the outcomes of the re-examination by the EMA.

UK: Advice on switching between different manufacturers' anti-epileptic drugs

On 12 November 2013, the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK issued new guidance to healthcare professionals in relation to anti-epileptic drugs (AEDs). This follows a review by the Commission on Human Medicines (CHM) which looked at the evidence on patients switching between different manufacturers' products of particular AEDs.

CHM concluded that whilst there was no clear evidence of harm associated with switching products, an effect in some patients, for some drugs, could not be completely ruled out. The potential effects of switching products may include a loss of seizure control or the occurrence of side effects, or both. These risks can be associated with switching between a branded originator and a generic product, and between different generic products.

CHM advised that AEDs could be classified into three categories. This aimed to help healthcare professionals to decide on whether maintaining a continuous supply of a specific manufacturer's product is necessary.

> Category 1: For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product. They are phenytoin, carbamazepine, phenobarbital and primidone.
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> Category 2: For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer taking into account factors such as seizure frequency and treatment history. They are valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide and topiramate.
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> Category 3: For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors. They are levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide and vigabatrin.

In Hong Kong, there are 155 registered pharmaceutical products belonging to AEDs of ingredients:

> Category 1 - phenytoin, carbamazepine and phenobarbitone

Category 2 - valproate, valproic acid, lamotrigine, retigabine, clobazam, clonazepam, oxcarbazepine and topiramate

Category 3 - levetiracetam, lacosamide, gabapentin, pregabalin and vigabatrin

All of the products are prescription only medicines. In view of MHRA's latest advice, a letter to healthcare professionals was issued on 13 November 2013. DH will keep vigilant on any safety updates of the drugs.

Health Canada: Risperidone- or paliperidone-containing products associated with intraoperative floppy iris syndrome

On 14 November 2013, Health Canada announced about the risk of intraoperative floppy iris syndrome (IFIS) associated with the use of risperidone- or paliperidone-containing products. These products are primarily prescribed for the treatment of schizophrenia; however, the risk applies to all patients undergoing cataract surgery, who have been exposed to these products, irrespective of indication.

According to Health Canada, cases of IFIS had been reported with the use of risperidone. Although there was no reports received with the use of paliperidone, since paliperidone is the major active metabolite of risperidone and they are pharmacologically very similar, a risk of IFIS in patients undergoing cataract surgery and receiving paliperidone cannot be excluded.

IFIS is a recently described intraoperative complication that has been observed during cataract surgery in patients receiving risperidone. IFIS is characterized by a triad of intraoperative signs (billowing of a flaccid iris stroma, progressive intraoperative pupil constriction and a propensity for iris prolapse) that may present with varying degrees of severity and is associated with an increased rate of cataract surgical complications. Cataract surgeons are therefore advised to inquire about current or prior use of risperidone- or paliperidone-containing products in patients and approach the surgery with caution. If IFIS is suspected, modifications to surgical technique may be required.

In Hong Kong, there are 77 registered pharmaceutical products containing risperidone and 8 containing paliperidone. All of them are prescription only medicines indicated for the treatment of schizophrenia. DH had not received any adverse reaction report on intraoperative floppy iris syndrome and other ophthalmic adverse events in relation to risperidone and paliperidone so far. In view of Health Canada's announcement, a letter to healthcare professionals was issued on 15 November 2013, and the matter will be discussed in the meeting of the Registration Committee.

US: Lexiscan (regadenoson) and Adenoscan (adenosine) associated with rare but serious risk of heart attack and death

On 20 November 2013, FDA warned healthcare professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents Lexiscan (regadenoson) and Adenoscan (adenosine). FDA had approved changes to the drug labels to reflect these serious events and updated recommendations for use of these agents. At this time, there is insufficient data to determine whether there is a difference in risk of heart attack or death between Lexiscan and Adenoscan.

Health care professionals should avoid using these drugs in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions. They are advised to screen all nuclear stress test candidates for their suitability to receive Lexiscan or Adenoscan. It is important that cardiac resuscitation equipment and trained staff should be available before administering Lexiscan or Adenoscan.

In Hong Kong, there is one registered pharmaceutical product containing adenosine, namely Adenoscan Inj 3mg/ml (HK-43112) and none with regadenoson. It is a coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate. In view of FDA's recommendations, a letter to healthcare professionals was issued on 21 November 2013, and the matter will be discussed in the meeting of the Registration Committee.

The Mainland: Fluoroquinolones associated with serious adverse reactions

On 21 November 2013, the China Food and Drug Administration (CFDA) alerted about serious adverse reactions associated with fluoroquinolones. Various surveillance data from China and other countries and related literatures indicated that fluoroquinolones with neuromuscular blocking activity may aggravate the symptoms of myasthenia gravis in patients with myasthenia gravis and may cause peripheral neuropathy. The risk of peripheral neuropathy may occur soon after these drugs are taken and may be permanent. Individual fluoroquinolones may also affect the level of glycemic control in diabetic patients, and the risk of hypoglycaemia differs among these drugs, in which moxifloxacin is of the highest risk.

In Hong Kong, there are 253 registered pharmaceutical products belonging to fluoroquinolones of ingredients besifloxacin, ciprofloxacin, enrofloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, norfloxacin, ofloxacin, prulifloxacin and sparfloxacin. They are prescription only medicines indicated for the treatment of adults with various bacterial infections such as infections of the respriatory tract, skin and urinary tract. Safety alerts regarding the risk of myasthenia gravis associated with fluoroquniolones had been released by Health Canada, and were reported in Drug News Issue No. 25 and 29. The matter was discussed by the Registration Committee in February 2012 and the decision made by the Registration Committee was reported in Drug news Issue No. 29. Safety alerts regarding the risk of permanent nerve damage associated with fluoroquniolones had been released by FDA and was reported in Drug News Issue No. 46. The matter was discussed by the Registration Committee in its meeting in December 2013. The Registration Committee decided that the sales pack labels and/or package inserts of products containing fluoroquinolones should include the following new safety information:

> *"Peripheral Neuropathy*
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> *Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones. Symptoms may occur soon after initiation of fluoroquinolones and may be irreversible. Fluoroquinolones should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation."*

US: Rosiglitazone-containing diabetes medicines - removal of some prescribing and dispensing restrictions

On 25 November 2013, FDA announced that recent data for rosiglitazone-containing drugs do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, FDA is requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on FDA review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI).

Previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an elevated risk of heart attack, so FDA required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The Rosiglitazone REMS program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks. Although there are still some scientific uncertainty about the cardiovascular safety of rosiglitazone, FDA's concern has been substantially reduced with the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. The rosiglitazone REMS program requirements will therefore be modified as well as the rosiglitazone prescribing information and the patient Medication Guide be revised to include the new information. The proposed modifications to the rosiglitazone REMS program include:

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- Distribution of the medicines will no longer be restricted. Rosiglitazone may be used along with diet and exercise to improve control of blood sugar in patients with type 2 diabetes mellitus.
- Health care professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone REMS program to be able to prescribe, dispense, or receive rosiglitazone medicines.
- As part of the REMS, sponsors will ensure that health care professionals who are likely to prescribe rosiglitazone medicines are provided training based on the current state of knowledge concerning the cardiovascular risk of rosiglitazone medicines. Manufacturers will also send Dear Healthcare Provider and Dear Professional Society letters to educate prescribers about the new information.

In Hong Kong, there are eight registered pharmaceutical products containing rosiglitazone, namely Avandia Tiltab Tab 2mg (HK-47006), 4mg (HK-47007), 8mg (HK-47008), Avandamet Tab 1mg/500mg (HK-51300), 2mg/500mg (HK-51301), 4mg/500mg (HK-51302), 4mg/1000mg (HK-53135) and 2mg/1000mg (HK-53136). All products are registered by GlaxoSmithKline Ltd. (GSK) and are prescription only medicines. Currently, only Avandia Tiltab Tab 4mg (HK-47007) is marketed in Hong Kong. Rosiglitazone is a thiazolidinedione used for the treatment of Type II diabetes. The safety concern of rosiglitazone in increasing cardiovascular risks had been reviewed worldwide and has been reported Drug News Issue No. 7, 10, 12 and 20. On 4 October 2010, the Registration Committee decided to restrict the use of rosiglitazone and revise the product package insert accordingly. DH also issued a press statement and letters to healthcare professionals on the same day regarding this recommendation. The Registration Committee also decided at its meeting on 15 June 2011 to request GSK to provide the details of the restricted access and distribution program implemented in USA, namely Avandia-Rosiglitazone Medicines Access Program, and submit a proposal of a similar restricted access and distribution program to be used in Hong Kong for the Committee's consideration. Subsequently, GSK has proposed a similar restricted program, the Rosiglitazone-containing Medicines Access Program (RAP), in Hong Kong and the Registration Committee agreed with the proposed RAP in its meeting on 5 December 2012. DH will remain vigilant on further new safety updates on rosiglitazone by other overseas health authorities for consideration of any necessary actions by the Registration Committee.

Drug Recall

Recall of OPSA-HIS Sterile Eye Drops

On 18 November 2013, DH instructed a licensed drug wholesaler, Nidoway Investment Ltd, (Nidoway), to recall a batch of OPSA-HIS Sterile Eye Drops (registration number: HK-51055, batch number 120072) from the market due to quality issue.

Under the DH's market surveillance, the content of one of the drug ingredients of the eye drops, namely antazoline, was found to be lower than the labelled amount. The product is an over-the counter medicine used for relief of eye allergy.

Preliminary information revealed that 2,000 bottles of the affected batch were imported in May 2012 from the Thailand manufacturer, Thai P.D. Chemicals Co. Ltd. All of the which had been supplied to pharmacies and medicine shops. There is no evidence suggesting that other batches of the product are affected.

DH had closely monitored the recall. A press statement was released on the same day to alert the public of the recall. Members of the public who have purchased the above product should stop using it immediately and consult healthcare professionals if in doubt.

Drug Incident

Man arrested for suspected illegal sale of slimming product with controlled ingredient on the Internet

On 7 Novemebr 2013, a joint operation was conducted by DH and the Police in Mong Kok resulting in the arrest of a 49-year-old man for suspected illegal sale of a slimming product labelled as containing a Part I poison. The slimming product in question is called Fat Burner. It was labelled as containing DNP (dinitrophenol), a chemical which can be dangerous to health. Acting on intelligence, it was found that the above product was being offered for sale on the Internet.

Dinitrophenol is a Part I poison which has been used as a herbicide. It is an industrial chemical and is not fit for human consumption. When consumed, dinitrophenol can be extremely dangerous to human health, possibly leading to coma and death. Signs of acute poisoning include nausea, vomiting, dizziness and irregular heartbeat. According to the UK Food Standards Agency, there had been cases of death of young people after they had taken the substance. A press statement was released on the same day to alert the public of the incident.

Retail shop raided for suspected illegal sale of unregistered pharmaceutical products with controlled drug ingredients

On 15 November 2013, a joint operation was conducted by DH and the Police against retail shop in Tsim Sha Tsui resulting in the arrest of a 36-year-old woman for suspected illegal sale of unregistered pharmaceutical products with controlled drug ingredients.

Upon the investigation of a public complaint, DH found various suspected unregistered pharmaceutical products being offered for sale by the retail shop. The products were labelled in Japanese as containing various Part I poisons including neostigmine, felbinac, dihydrocodeine, ibuprofen, fluocinolone and an antibiotic, neomycin. Hong Kong pharmaceutical product registration numbers were not found on any of the product labels. Preliminary investigation had so far revealed that the products were sourced by the company outside Hong Kong.

Inappropriate use of steroids like fluocinolone may cause serious side effects, such as Cushing's Syndrome with symptoms including moon face and muscle atrophy, while inappropriate use of antibiotics may lead to antibiotics resistance. Taking painkillers such as felbinac and ibuprofen without medical supervision may lead to gastrointestinal bleeding. Products with the ingredients dihydrocodeine and neostigmine may cause nausea and vomiting. Members of the public should not self-medicate without advice from healthcare professionals. A press statement was released on the same day to alert the public of the 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 I poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part I 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.

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.

Useful Contact

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Adverse Drug Reaction (ADR) Reporting:

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