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Adverse Drug Reaction News

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New contraindication on the use of high-dose diclofenac for more than four weeks in selected groups of patients

HSA would like to inform healthcare professionals that the use of high-dose systemic diclofenac (150mg/day via oral, rectal or parenteral routes) for more than four weeks is contraindicated in patients with established cardiovascular (CV) disease or uncontrolled hypertension. This regulatory decision was made following HSA's benefit-risk assessment, in consultation with its Product Vigilance Advisory Committee (PVAC) and several other clinical experts.

Background

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that has been licensed in Singapore since February 1991 for the treatment of pain and inflammation for a wide range of conditions including rheumatism, post-traumatic pain and post-operative pain. There are more than 30 different brands of diclofenac registered locally.

HSA has been closely monitoring the CV safety of NSAIDs since 2005. A Dear Healthcare Professional Letter was issued on 28 April 2005 following HSA's benefit-risk assessment and the conclusion that there was a small but increased CV risk with NSAIDs.[1] Healthcare professionals were recommended to prescribe NSAIDs at the lowest effective dose and for the shortest possible duration required for treatment. In addition, it was advised that all NSAIDs should not be prescribed in patients who have undergone recent coronary artery bypass surgery and revascularisation procedures.

Benefit-risk assessment of systemic diclofenac

In recent years, there has been a growing body of scientific evidence to suggest that high doses of diclofenac used over a long duration is associated with increased CV risks.[2-5] In a meta-analysis conducted by the Coxib and traditional NSAID Trialists' Collaboration, the risk of major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) was reported to have increased by about a third in patients receiving a selective COX-2 inhibitor (rate ratio [RR] 1.37; 95% CI 1.14, 1.66; p=0.0009) or diclofenac (RR 1.41; 95% CI 1.12, 1.78; p=0.0036), when compared with placebo.[2] This was mainly due to an increase in major coronary events such as non-fatal myocardial infarction or coronary death (selective COX-2 inhibitor: RR 1.76; 95% CI 1.31, 2.37; p=0.0001; diclofenac: RR 1.70; 95% CI 1.19, 2.41; p=0.0032).

International regulatory actions

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) completed a safety assessment in June 2013, which concluded that benefits of systemic diclofenac still outweigh the risks but there is an increase in CV risk in patients taking systemic diclofenac at high doses over a long period. PRAC recommended that the precautions already in place in the European Union to minimise the risk of arterial thromboembolic events with selective COX-2 inhibitors should also be applied to diclofenac. These precautions include a contraindication in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease. The Committee also recommended that patients with significant risk factors for CV events be treated with diclofenac only after careful consideration.[6]

In July 2013, the New Zealand Medicines and Medical Device Safety Authority's benefit-risk assessment concluded that there is a small increase in CV risk with the use of high-dose diclofenac when given over a long duration. The New Zealand authority reminded its healthcare professionals to prescribe diclofenac at the lowest effective dose for the shortest possible duration and advised against using diclofenac in patients who have had a recent myocardial infarction (within the last 6 to 12 months).[7]

HSA's advisory

Taking into consideration the currently available scientific evidence, expert opinions from local clinicians and HSA's PVAC, as well as the regulatory developments in other international jurisdictions, HSA is advising healthcare professionals on the following:

- The use of high-dose systemic diclofenac (150mg/day) for more than four weeks is contraindicated in patients with established CV disease (congestive heart failure, established ischaemic heart disease, peripheral arterial disease) or uncontrolled hypertension.
- If systemic diclofenac treatment is needed, patients with established CV disease, uncontrolled hypertension or significant CV risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100mg daily if the treatment is for more than 4 weeks.
- As the CV risks of systemic diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible.

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Risk of Intraocular Floppy Iris Syndrome (IFIS) with risperidone or paliperidone in patients undergoing cataract surgery

HSA would like to alert healthcare professionals to the risk of intraoperative floppy iris syndrome (IFIS) observed during cataract surgery in patients treated with risperidone or paliperidone.

Risperidone and paliperidone are antipsychotic drugs used for the treatment and management of schizophrenic conditions. The innovator drugs, Risperdal® (risperidone) and Invega® (paliperidone), have been registered in Singapore since 1995 and 2007, respectively, and are marketed by Johnson & Johnson Pte Ltd. There are also 17 generic risperidone products registered locally.

Background

IFIS has been observed during cataract surgery in patients on α-adrenergic antagonists.[1] It is characterised by a triad of intraoperative signs (billowing of a flaccid iris stroma, progressive intraoperative pupil constriction, propensity for iris prolapse towards the phaco and side port incisions) that may vary in severity. IFIS is also associated with an increased rate of complications during cataract surgery (e.g., iris trauma, posterior capsule rupture, and vitreous loss), as well as postoperative complications of increased intraocular pressure and cystoid macular oedema.

During routine pharmacovigilance surveillance by Johnson & Johnson, six cases of IFIS associated with the use of risperidone were identified from a review of postmarketing safety data, of which two reported a plausible relationship between risperidone treatment and IFIS. In both cases, the patients had received long-term treatment with risperidone and developed typical features of IFIS during cataract surgery. A positive re-challenge was demonstrated in one of the cases where IFIS recurred in the second eye during cataract surgery four months later with continued risperidone treatment.

As risperidone is a selective monoaminergic antagonist with a high affinity for α1-adrenergic receptors, there exists a possible biological plausibility of its association with IFIS. This adverse event is very rare, being estimated at approximately 1 per 7 million person-years of treatment. The association is also extended to paliperidone since it is the active metabolite of risperidone and therefore shares similar pharmacological and safety profiles. However, to date, the company has not received any reports of IFIS associated with paliperidone.

Local Situation & HSA's advisory

A Dear Healthcare Professional Letter, issued by Johnson & Johnson on 7 January 2014, was disseminated to psychiatrists and ophthalmologists to provide information on this emerging risk. The letter included the following advisories:

- It is recommended that cataract surgeons ask patients about current or prior use of risperidone or paliperidone when taking a medication history preoperatively.
- If IFIS is suspected, modifications to surgical technique may be required and the cataract surgery should be approached with caution.
- The potential benefit of stopping α1-adrenergic receptor blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

This safety information has been updated in the package inserts (PIs) of all Risperdal® and Invega® products. The PIs of generic risperidone-containing products will be strengthened to include this new safety alert.

Although no local reports of IFIS associated with risperidone or paliperidone have been received by HSA, healthcare professionals are advised to document the use of α1-adrenergic antagonists, including risperidone and paliperidone, when making a referral for cataract surgery.

Healthcare professionals are also encouraged to report any cases of IFIS suspected to be associated with risperidone or paliperidone to the Vigilance Branch of HSA.

Reference

1 *Ophthalmology 2009; 116: 658-63*

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New contraindication on the use of high-dose diclofenac for more than four weeks in selected groups of patients

A Dear Healthcare Professional Letter was issued on 27 February 2014 to healthcare professionals to inform them on the new contraindication and updated advisories.[8] The local package inserts for systemic diclofenac-containing products will be strengthened to reflect these recommendations.

Healthcare professionals are encouraged to take into consideration the above recommendations when prescribing diclofenac. They are also encouraged to report any suspected serious adverse reactions related to diclofenac to the Vigilance Branch of HSA.

References

1 *http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL/2005.html*
2 *Lancet 2013; 382: 769-79*
3 *Cir Cardiovasc Qual Outcomes 2010; 3: 395-405*
4 *Pharmacoepidemiol Drug Saf 2013; 22: 559-70*
5 *PLoS ONE 2013; 8: e54309*
6 *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diclofenac-containing_medicinal_products/European_Commission_final_decision/WC500155819.pdf*
7 *http://www.medsafe.govt.nz/Projects/B2/2013/diclofenac-cardio.asp*
8 *http://www.hsa.gov.sg/DHCPL*

AE case in focus: Test yourself

An adult male, who had previously been prescribed an antiretroviral drug cocktail of tenofovir, lamivudine and efavirenz, was switched to abacavir 600mg, lamivudine 300mg and efavirenz 600mg due to nephrotoxicity. After taking abacavir for one week, the patient started experiencing mild diarrhoea which gradually became more severe, along with fever and shortness of breath on exertion. Upon admission to hospital, he was noted to have developed a generalised rash on his trunk, accompanied by nausea, vomiting, as well as four episodes of watery, non-bloody and non-mucoid diarrhoea per day. Chest X-ray was negative and airway blood gas and blood counts were unremarkable. The attending doctor also noted worsening acute renal failure and transaminitis.

a) What could be the suspected adverse drug reaction and the likely drug associated with it?
b) What are the risks of re-challenging the patient with the suspected drug?

This case is based on an actual adverse event report submitted to HSA, but with minor changes to protect patient confidentiality. We would like to take this opportunity to thank Dr James Molton and Dr Sophia Archuleta, Division of Infectious Disease, National University Hospital for their contributions to drug safety education.

Answers to the case study can be found on page 6.

Risk management strategies by HSA
Restricted Access Programme and provision of educational materials

The Vigilance Branch of HSA implements several risk minimisation activities which are targeted at mitigating the known risks of health products to safeguard public health. Examples of such activities include issuance of communication and educational materials to healthcare professionals, controlled distribution of the health products to selected physicians or pharmacies, maintenance of patient registry, special product packaging, additional labelling, and the 'Restricted Access Programme'. Two of such risk mitigation strategies are highlighted here – the 'Restricted Access Programme' and provision of educational materials to physicians and/or patients.

1) Restricted Access Programme

The 'Restricted Access Programme' is introduced for medicinal products that are associated with significant safety issue(s) that affect(s) their overall benefit-risk profile but are still beneficial for a selected group of patients with no suitable therapeutic alternatives. This allows for continued use of the medicinal product in the local market while ensuring that adequate measures are in place to mitigate its risks.

This programme requires the product licence holder to supply the medicinal products only to doctors who have signed a letter of undertaking. In this undertaking, doctors indicate that they:

i) are aware of the potential serious adverse reactions associated with the use of the medicinal product,

ii) will only prescribe the medicinal product to patients whom they have assessed to have no other suitable therapeutic alternatives,

iii) will obtain informed patient consent on the use of the medicinal product after counselling their patients on the potential risks involved,

iv) will monitor their patients closely for adverse reactions and to report any serious adverse reactions associated with the medicinal product to HSA.

In addition, the product licence holder is required to submit sales data to HSA regularly to facilitate the estimation of patient exposure. To date, there are three drugs placed on this programme, namely tegaserod (Zelmac®), aprotinin (Trasylol®) and rosiglitazone-containing products (Avandia®, Avandamet®).

2) Educational Materials

During pre-market or post-market safety reviews, some medicinal products may be identified to be associated with safety issues that could be prevented or minimised with close monitoring. Under such circumstances, educational materials are provided to physicians and/or patients to help inform them of potential risks associated with the use of these medicinal products and to educate on the early detection of adverse reactions. Either the Physician Educational Material (PEM) or Patient Medication Guide (PMG), or both, may be required depending on the nature of the issue.

PEM is a collective term used to describe all materials meant to inform physicians of the safety concerns associated with the product and the recommendation to perform specific monitoring or counselling when patients are prescribed the medication.

PMGs are materials requested by HSA for specific medicinal products which are associated with potential safety issues. HSA has assessed that these are safety issues that may be mitigated with self-monitoring. These medication guides are developed to provide information to teach patients how to monitor themselves for occurrence of potential side effects and when to seek help from medical professionals. PMGs are to be given to all patients who are prescribed the medication, and can come in the form of reading materials or an alert card. PMGs are different from Patient Information Leaflets (PIL) that are available with the package inserts of some products, as the PMG is developed in consultation with HSA to address specific safety concerns with the intention of risk mitigation.

The table below lists the products with PEM and/or PMG approved by HSA to date. Healthcare professionals may approach the companies marketing these products for the relevant educational materials.

- Benlysta (GSK)^
- Botox (Allergan)
- Brinavess (MSD)^
- Dynastat (Pfizer)
- Effient (Eli Lilly)^
- Evoltra (Sanofi-Aventis)
- Exjade (Novartis)
- Gilenya (Novartis)
- Kadcyla (Roche)^
- Multaq (Sanofi-Aventis)
- Nivestim (Hospira)^
- Nplate (Kyowa Hakko Kirin)
- Pradaxa (Boehringer Ingelheim)
- Priligy (A. Menarini)
- Protos (Servier)#
- Revlimid (Celgene)
- Revolade (GSK)
- Scitropin A (Scigen)
- Soliris (A. Menarini)
- Tarceva (Roche)
- Tysabri (UCB Trading)
- Valdoxan (Servier)^
- Vectibix (GSK)^
- Velcade (Johnson & Johnson)^
- Victrelis (MSD)^
- Xarelto (Bayer)

^*only PEM available*
#*only PMG available*

Healthcare professionals are encouraged to refer to the PEM for reminders on special monitoring or counselling requirements for specific medicinal products, and to provide their patients with the PMG (if available) when counselling them on potential adverse reactions associated with the product.

Analysis of adverse event reports for Year 2013

In 2013, the Vigilance Branch (VB) of HSA reviewed 19,885 valid local adverse event (AE) reports suspected to be associated with health products, making Singapore the country with the highest number of reports (based on per million inhabitants) submitted to the World Health Organisation (WHO) global pharmacovigilance database (Figure 1). Singapore has maintained this position since 2011.

Of these, 96.8% were associated with pharmaceuticals, 1.5% with vaccines, 1.0% with biologics, and 0.7% with complementary health products (CHPs), which includes Chinese Proprietary Medicines, health supplements, other traditional medicines, and cosmetics. Public hospitals (49.2%) and polyclinics (47.7%) contributed to the majority of these reports, followed by drug companies (2.1%) and private clinics/hospitals (1.0%). While doctors remain the top contributors of AE reports (85.7%), reports from pharmacists are on an increasing trend (from 4.7% in 2010 to 10.3% in 2013). Other contributors of AE reports included drug companies, dentists, nurses, research coordinators and TCM practitioners.

An analysis of the AE reports showed that there were more AEs reported in females (56.8%) than in males. In terms of age, 43.8% of the AEs were reported to occur in patients aged 50 years and older. Skin-related disorders were the most commonly reported AE (50.8%), followed by those that affect the body as a whole (e.g., general disorders such as pain, fever, oedema) (18.0%) and respiratory disorders (e.g., coughing, shortness of breath) (6.9%). Drugs suspected of causing serious adverse reactions of the blood, liver and skin are listed in Table 1. To communicate important safety issues to healthcare professionals, a total of 62 Dear Healthcare Professional Letters (DHCPLs) were issued last year.

Drug-AE pairs of interest

The AE reports submitted to HSA are entered into the national AE database. VB regularly analyses these data for detection of potential safety signals and would like to highlight some examples of serious AEs reported.

1 Omeprazole: Risk of Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

Omeprazole, a proton-pump inhibitor, is commonly used for gastroprotection and treatment of gastrointestinal ulcers. Given its wide usage locally, VB would like to highlight the rare but serious risk of Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) associated with the use of omeprazole. Of the 43 AE reports of omeprazole-associated SJS/TEN received from 2000 to January 2014, 16 listed omeprazole as the only suspected drug. The patients in these reports ranged from 10 to 90 years old, with a median age of 66 years. The majority of the SJS/TEN cases occurred within six weeks of starting omeprazole. Twelve patients died as a result of complications arising from the AE, with many being complex cases with some form of pre-existing conditions (e.g., cancer, diabetes, renal impairment).

2 Dabigatran (Pradaxa®): Thromboembolic events and increased risk of bleeding

Dabigatran, an oral direct thrombin inhibitor, is indicated for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation and prophylaxis of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

VB has been closely monitoring AEs associated with dabigatran. As of early February 2014, VB has received a

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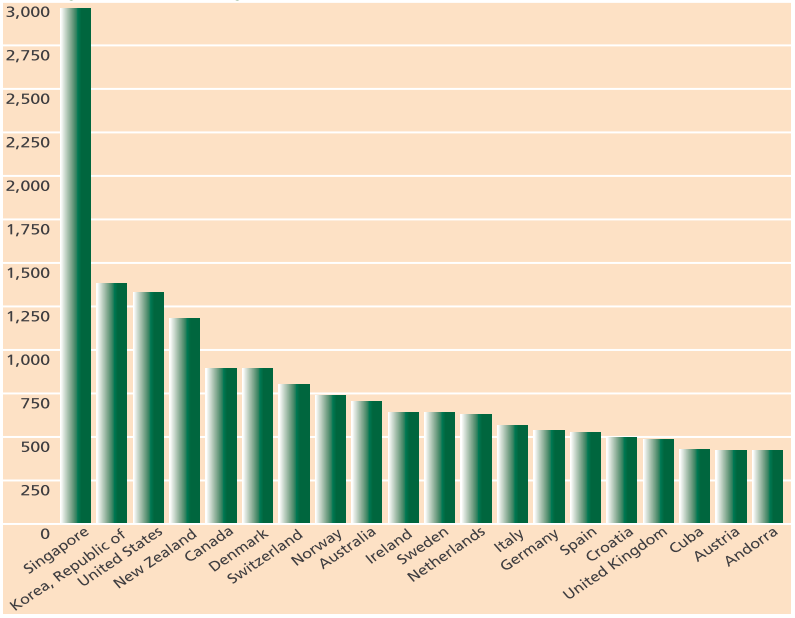
Figure 1. Active Individual Case Safety Reports (ICSRs) in the WHO global ICSR database (per million inhabitants and year) for the period covering January 2009 to January 2014



[Reproduced with permission from Uppsala Monitoring Centre]

Table 1. Drugs suspected of causing serious AEs

Description	WHO preferred term	Suspected active ingredient(s) *(the number in the bracket represents the number of times the drug has been implicated#)*
Skin disorders	Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)/SJS-TEN	Carbamazepine (9)*, Cotrimoxazole (7), Allopurinol (6), Omeprazole (6), Vancomycin (5), Ceftriaxone (3), Dapsone (3), Paracetamol (3), Amoxicillin (2), Bendamustine (2), Doxycycline (2), Iohexol (2), Lamotrigine (3), Mefenamic acid (2), Meropenem (2), Phenytoin (3), Piperacillin and Tazobactam (2), Risperidone (2), Rituximab (2), Sulfasalazine (2)
Body as a whole	Drug Hypersensitivity Syndrome	Phenytoin (6), Allopurinol (5), Cotrimoxazole (5), Omeprazole (2), Vancomycin (2)
Blood disorders	Agranulocytosis/ neutropenia/ neutropenic sepsis	Azathioprine (3), Clozapine (3), Deferiprone (3), Lenalidomide (3), Carbimazole (2), Methimazole or Thiamazole (2), Mycophenolate (2), Rituximab (2), Valproic acid (Valproate) (2)
	Leucopenia	Azathioprine (3), Phenytoin (2), Quetiapine (2), Sulfasalazine (2)
	Pancytopenia	Cotrimoxazole (2)
	Thrombocytopenia	Heparin (7), Valproic acid (Valproate) (7), Phenytoin (3), Cotrimoxazole (2), Piperacillin and Tazobactam (2), Trastuzumab emtansine (2), Vancomycin (2)
Hepatic disorders	Hepatitis/Hepatitis Cholestatic/Jaundice Hepatotoxic effect	Azathioprine (5), Coamoxiclav (4), Phenytoin (4), Simvastatin (4), Ketoconazole (3), Ciprofloxacin (2), Isoniazid (2), Regorafenib (2)

 # More than one suspected drug may be implicated in a single AE report. Only active ingredients implicated more than once are listed here.

** After the implementation of HLA-B*1502 genotype screening as standard of care for new carbamazepine (CBZ) patients of Asian ancestry on 30 April 2013, HSA has not received any reports of SJS/TEN associated with the use of CBZ in patients screened for the HLA-B*1502 allele.*

Caveat for interpreting the AE figures

AE reports describe an AE that has occurred in association with a drug but does not necessarily mean that the drug has been determined to be the cause of the AE. Many other factors need to be taken into account in assessing causal relationships and these include the presence of underlying diseases and medical conditions and the possible contribution of concomitant medicines.

It is worthwhile to note that the volume of AE reports for a particular drug may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time. Therefore the reports should not be used to determine or measure the frequency of an AE.

Table 2. Top 6 vaccines suspected to cause VAEs in children

Ranking	Type of vaccine	Total number of reports received#	Examples of some serious VAEs *(number of reports received)*
1	*Bacillus Calmette-Guérin* (BCG)	105	Lymphadenitis (70), injection site abscess (3), BCG osteomyelitis (1)
2	Measles, Mumps and Rubella (MMR)	36	Seizure (22), thrombocytopenia (6), Gianotti-Crosti Syndrome (1), Kawasaki disease (1)
3	Pneumococcal conjugate (PNC)	30	Seizure (12), thrombocytopenia (4), Kawasaki disease (2), vaccine failure (2), Gianotti-Crosti Syndrome (1), *Henoch-Schönlein purpura* (1), injection-site cellulitis (1)
4	5-in-1*	28	Seizure (8), Kawasaki disease (7), thrombocytopenia (3), injection-site cellulitis (3), injection-site haematoma (1)
5	Measles, mumps, rubella and varicella (MMRV)	24	Seizure (14), vaccine failure (4), thrombocytopenia (3)
6	Rotavirus	14	Gastroenteritis or diarrhoea (4), intussusception (3), haematochezia (1), Kawasaki disease (1), seizure (1), thrombocytopenia (1), vaccine failure (1)

\# *More than 1 vaccine may be implicated for each VAE report*

* *5-in-1 includes Diphtheria, Pertussis, Tetanus, inactivated Polio and Haemophilus influenza type B vaccines*

total of 32 AE reports associated with dabigatran. Of these, nine were associated with thromboembolic events (e.g., stroke). Another nine reported bleeding, including one case of cardiac tamponade due to hemopericardium in a chronic renal failure patient, despite using a reduced dose of dabigatran at 75mg twice daily. Many of these AE reports contained limited information, and analysis of age, renal impairment and concurrent medications (e.g., antiplatelets) did not yield any significant results.

The increased risk of bleeding with dabigatran could be precipitated by a number of factors: (i) deterioration of renal function (hence affecting renal clearance of the drug), (ii) concurrent use of antiplatelets and NSAIDs, or (iii) drug interactions which potentiate the effects of dabigatran. To address the practical issues of using novel oral anticoagulants (NOACs) such as dabigatran, the Chapter of Haematologists, College of Physicians Singapore, has recently convened a workgroup and formulated a consensus opinion on the prevention and management of bleeding complications associated with NOACs. Healthcare professionals may refer to the recommendations for further information.[1]

3 Ertapenem (Invanz®): Risk of central nervous system AEs (including seizures)

The association between carbapenems, a class of broad spectrum antibiotics, and central nervous system (CNS) AEs are known and expected. However, a disproportionately higher number of reports of CNS AEs associated with ertapenem compared to other carbapenems had been observed in our database.

Of the 102 AE reports associated with ertapenem received up till January 2014, 49 (48.0%) reported CNS AEs, including 23 cases of seizures. The other CNS AEs reported included confusion, delirium, altered mental status and psychosis. In contrast, there were only four and nine reports of CNS AEs (including seizures) associated with meropenem and imipenem/cilastatin, respectively. Local sales data of carbapenems could not account for this disproportionality.

An analysis of these reports revealed that most of these AEs occurred in the elderly, those with a history of CNS disorders, and in renal-impaired patients. Of the 49 cases of ertapenem-associated CNS AEs, 11 (22.4%) patients were reported to have some degree of renal impairment, or had their ertapenem doses adjusted for renal impairment. The time-to-onset ranged from 2 to 11 days for seizures and 0 to 10 days for other CNS AEs.

Vaccine adverse event (VAE) reports

HSA has continued working with KK Women's and Children's Hospital on active surveillance of paediatric vaccine adverse events (VAEs), which contributed to 88% of the total VAE reports in children below 12 years of age. In 2013, a total of 289 VAE reports were received, of which 36 (12%) involved more than one vaccine. The commonly reported vaccines suspected to cause VAEs in children are listed in Table 2.

The reports of lymphadenitis associated with *Bacillus Calmette-Guérin* (BCG) vaccine involved children who were vaccinated between 2009 and 2013. A breakdown of the reports by yearly vaccinated cohort showed a higher number of cases observed with the 2011 vaccinated cohort, followed by a downtrend thereafter. The local incidence of BCG-associated lymphadenitis remained within the expected values seen globally.

There were more reports of febrile seizures associated with pneumococcal conjugate (PNC) vaccine in 2013 (12 reports), as compared to four reports in 2012. The majority of these cases (8 reports) involved the concomitant administration of measles, mumps and rubella (MMR) or measles, mumps, rubella and varicella (MMRV) vaccine with the PNC vaccine.

Other commonly reported vaccines suspected to cause VAEs in children above 12 years of age and adults were associated with the seasonal influenza vaccine (24 reports), tetanus toxoid vaccine (15) and human papillomavirus (HPV) vaccine (9). The majority (73%) of these reports were non-serious. The remaining cases reported as serious included isolated cases of reactive arthritis and hypersensitivity reaction with the seasonal influenza vaccine, anaphylactic shock with the tetanus toxoid vaccine, and Henoch-Schönlein purpura and syncope with the HPV vaccine.

AEs associated with complementary health products

There were a total of 136 AE reports involving complementary health products (CHPs) including Chinese Proprietary Medicines (20 reports), health supplements (74), complementary medicines (42) and cosmetics (3). Some of the AE reports were associated with more than one suspected product.

Of the 74 reports describing hypersensitivity reactions, 66.2% were associated with glucosamine preparations and considered non-serious (e.g., rash, pruritus). Another 14 reports described hepatic reactions (e.g., raised liver enzymes, jaundice). As liver injury caused by health products is usually a diagnosis of exclusion, the presence of confounding medications and pre-existing conditions in most cases makes it difficult to ascertain a definitive causality between the suspected products and hepatic reactions. Moreover, herbs are often used in various combinations, doses and duration, making it difficult to isolate the component(s) which might have caused the hepatic reaction.

Through the vigilance of astute clinicians, HSA also managed to uncover 21 adulterated CHPs and issued four press releases to alert the public to the dangers of illegal health products. Most adulterated CHPs were marketed as tablets/capsules for pain relief or sexual enhancement/vigour, or as cosmetic products for skin whitening. Common adulterants included antihistamines, corticosteroids, sildenafil, NSAIDs, hydroquinone and/or mercury.

Acknowledgement

HSA would like to take this opportunity to thank all healthcare professionals for your active participation in the reporting of AEs. Your continuous vigilance and support are imperative towards our goals of detecting potential safety signals in a timely manner and taking actions to safeguard public health.

Reference

1 *Ann Acad Med Singapore 2013; 42: 593-602*

Attention Deficit Hyperactivity Disorder (ADHD) medications and risk of priapism

HSA would like to draw the attention of healthcare professionals to rare overseas reports of prolonged and painful erections (priapism) associated with the use of Attention Deficit Hyperactivity Disorder (ADHD) medications, namely methylphenidate and atomoxetine. The occurrence of this adverse event in relation to changes in dosage appeared to be inconsistent. Some cases occurred subsequent to an increase in methylphenidate dose, whereas others developed during periods of drug withdrawal (i.e. drug holidays or after discontinuation of treatment).

Methylphenidate and atomoxetine are both licensed locally for the treatment of ADHD. Methylphenidate is a central nervous system stimulant registered locally under the brand names Concerta® (Johnson & Johnson Pte Ltd), Ritalin® (Novartis (Singapore) Pte Ltd) and Rubifen® (Zyfas Medical Co). Atomoxetine (Strattera®, Eli Lilly (Singapore) Pte Ltd) is a selective norepinephrine reuptake inhibitor.

Published overseas case reports of priapism

Several case reports of priapism associated with methylphenidate have been reported in the literature.[1-4] In one article, a 12-year-old Caucasian boy was reported to have experienced prolonged and painful erections unaccompanied by sexual excitation for two years.[1] During these two years, he was treated with a starting dose of 18mg of methylphenidate which was subsequently increased to 36mg. The unwanted erections abated after methylphenidate was gradually reduced and subsequently stopped. In another case, the opposite effect was seen, where priapism occurred with missed doses. The 16-year-old boy, who was prescribed 54mg of extended-release methylphenidate daily for one year would experience priapism lasting for up to 24 hours whenever he missed a dose of his medication and the event would resolve after the drug was taken.[3] The mechanism of priapism associated with methylphenidate has not been understood but may be associated with methylphenidate's influence on multiple neurotransmitters.[1]

Review by the US Food and Drug Administration (FDA)

In December 2013, the US FDA issued a safety communication to warn of rare but serious cases of priapism associated with the use of methylphenidate.[5] This signal followed a safety review conducted by the FDA which took into consideration data from the FDA Adverse Event Reporting System and published literature. From 1997 to 2012, a total of 15 cases of priapism associated with methylphenidate were reported. The median age of these patients was 12.5 years (range 8 to 33 years). Of these cases, there were four patients who reported priapism following the withdrawal of methylphenidate and a few who reported the event after an increase in the drug dosage. In some patients, the event resolved after methylphenidate was restarted. There were cases where patients had to be hospitalised for treatment, including two patients who required surgical interventions such as shunt placement and needle aspiration of the corpus cavernosum.

In the safety communication, FDA similarly cautioned healthcare professionals that atomoxetine has also been associated with priapism. In fact, priapism appears to be more common with atomoxetine than methylphenidate and hence precautions on potential risk of priapism should be taken into consideration when patients are switched from methylphenidate to atomoxetine.

HSA's advisory

HSA has not received any local adverse reaction reports of priapism or sexual dysfunction associated with the use of methylphenidate or atomoxetine.

Healthcare professionals are advised to take into consideration the potential risk of priapism when prescribing methylphenidate or atomoxetine, or when switching their patients from methylphenidate to atomoxetine. Informing male patients and their caregivers about the risk of developing priapism and the signs and symptoms to look out for may help promote seeking of timely medical attention if priapism develops.

HSA is working with the companies to strengthen the package inserts of methylphenidate and atomoxetine products to include information on the risk of priapism. Healthcare professionals are encouraged to report local adverse reactions of priapism or sexual dysfunction associated with ADHD medications to the Vigilance Branch of HSA.

References

1 *Turk J Pediatr 2010; 52: 430-4*
2 *J Pediatr Urol 2013; 9: e1-2*
3 *http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n3-eng.php#a3*
4 *J Pediatr 2004; 144: 675-6*
5 *http://www.fda.gov/Drugs/DrugSafety/ucm375796.htm*

Answers to AE case in focus: Test yourself

a) *Abacavir hypersensitivity reaction*
b) *Re-introduction of abacavir in a patient with a history of hypersensitivity reaction to the drug has been reported to cause profound worsening of symptoms, including acute, severe hypersensitivity syndrome and death.*

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) indicated for the treatment of human immunodeficiency virus (HIV) infection. It is registered locally as Ziagen® (abacavir), Kivexa® (combination product of abacavir and lamivudine), and Trizivir® (combination product of abacavir, lamivudine and zidovudine). All three products are marketed by GlaxoSmithKline Pte Ltd.

Serious and sometimes fatal hypersensitivity reactions have been reported with the use of abacavir. Abacavir hypersensitivity reaction (HSR) is a non-specific, multi-organ syndrome characterised by two or more clinical signs and symptoms that include fever, rash, nausea, vomiting, headache, lethargy, myalgia or arthralgia, and respiratory and gastrointestinal symptoms.[1] These symptoms can occur any time during treatment with abacavir but usually appear within the first six weeks of therapy.[2]

The incidence rate of abacavir HSR has been reported at 5% in clinical studies and this risk is increased in patients with HLA-B*5701 allele carriage. In populations with similar HLA-B*5701 allele prevalence as the PREDICT-1 study population (i.e. 5.6% in a mainly white population[3]), it was estimated that 48% to 61% of patients with this allele will develop abacavir HSR during the course of abacavir treatment, as compared to 0% to 4% of HLA-B*5701 negative patients.[4] However, the PREDICT-1 study found that pre-therapy HLA-B*5701 screening could reduce the risks of immunologically confirmed abacavir HSR, with a negative predictive value of 100% and a positive predictive value of 47.9%.[3]

Our local HLA-B*5701 allele frequency is estimated at 6.3% in Indians, 1.8% in Malays and 1.1% in Chinese.[5] In 2008, the local package inserts were strengthened and an article published in the HSA ADR bulletin to highlight safety information regarding the increased risk of abacavir HSR with HLA-B*5701 allele carriage.[6] To date, five local cases of abacavir HSR have been reported to HSA.

As continuation of abacavir therapy or its re-challenge following abacavir HSR can lead to serious sequelae, it is recommended to discontinue this therapy in patients presenting with signs or symptoms suggestive of abacavir HSR until further assessment can be made. Alternative anti-retroviral therapies should be considered in these patients.

References

1 *Clin Ther 2002; 24: 1502-14*
2 *J Antimicrob Chemo 2007; 59: 591-3*
3 *N Engl J Med 2008; 358: 568-79*
4 *Singapore package insert for Ziagen® tablets, approved August 2012*
5 *Singapore Genome Variation Project HLA Data, Saw Swee Hock School of Public Health*
6 *HSA ADR News Bulletin 2008 Dec; 10: 3*

List of Dear Healthcare Professional Letters (DHCPL) issued by HSA, pharmaceutical and medical device companies since the last HSA ADR bulletin

For details, please log on to MOHAlert via your professional board's website.

Therapeutic products

4 Dec 2013 **Glibenclamide:**
Increased risk of severe and protracted hypoglycaemia in the elderly and renal-impaired

9 Dec 2013 **Xeloda® (capecitabine):**
Introduction of warnings and precautions for severe skin reactions

13 Dec 2013 **Zofran™ (ondansetron):**
Dose-dependent QT interval prolongation – updated information on dosage and administration for intravenous use in elderly

18 Dec 2013 **Protos® (strontium ranelate):**
Enhancing the awareness of the local risk management plan to mitigate the risk of serious skin reactions

23 Dec 2013 **Hydroxyethyl starch (HES)-containing products:**
Safety update on use in critically ill patients

9 Jan 2014 **Risperidone- or paliperidone-containing products:**
Risk of intraoperative floppy iris syndrome (IFIS) in patients undergoing cataract surgery

24 Jan 2014 **Kadcyla® (trastuzumab emtansine) and Herceptin® (trastuzumab):**
Potential risk for medication error resulting from name confusion

6 Feb 2014 **Mencevax ACWY™ (meningococcal vaccine):**
New antibody persistence data

7 Feb 2014 **Lamisil® (terbinafine):**
Package insert non-compliance for Lamisil Tablet 250mg 28's Batch W0012

11 Feb 2014 **Benlysta® (belimumab):**
Two post-marketing cases of Progressive Multifocal Leukoencephalopathy (PML) reported

17 Feb 2014 **Abraxane® (paclitaxel):**
Visible strands observed in intravenous infusion bag

27 Feb 2014 **Diclofenac:**
New contraindication on the use of high dose diclofenac for more than four weeks in selected groups of patients

10 Mar 2014 **Baxter range of intravenous solutions:**
Possible defect involving missing port protectors

12 Mar 2014 **Concerta™ (methylphenidate hydrochloride):**
Warning on potential risk of priapism

Medical devices

5 Dec 2013 **AMPLATZER Atrial Septal Occluder:**
Updates to Instructions for Use due to concerns of tissue erosion

10 Dec 2013 **ORCHESTRA and ORCHESTRA PLUS pacemaker programmer:**
Erroneous residual longevity displayed by programmer for pacemakers REPLY, ESPRIT and FACIL

11 Dec 2013 **CoreValve™ AccuTrak™ Delivery Catheter System:**
Updates to Instructions for Use due to reports of nose cone separation

14 Dec 2013 **Zimmer Trabecular Metal™ Reverse Shoulder System Glenosphere & Base Plate:**
Important information on the surgical technique specific to the assembly of the glenosphere to the base plate

19 Dec 2013 **Biomet 3i OSSEOTITE Dental Implants:**
Voluntary recall due to contact with residual machining fluid

30 Dec 2013 **Abbott Medical Optics Intraocular Lens:**
Brown discoloration of intraocular lens detected post-implantation

15 Jan 2014 **Zimmer® Segmental System Polyethylene Insert-Size B & Size C:**
Important information on the surgical technique and the Instruction for Use due to occurrence of hyper-extension

21 Jan 2014 **Uni-Elbow™ Systems and ReMotion™ Total Wrist Distal Radial Components:**
Voluntary recall of Lateral rHead Heads and Head Assemblies due to sterility breach

17 Feb 2014 **Model 8870 Software Application Card used in the 8840 N'Vision™ Clinician Programmer for SynchroMed Implantable Infusion System Therapy:**
Version update of software application card to correct issues of Erroneous Replace by Date and Premature Reservoir Alarm

17 Feb 2014 **Model 8870 Software Application Card used in the 8840 N'Vision™ Clinician Programmer to interrogate deep brain and spinal cord stimulators:**
Loss of stimulation and over stimulation issues with Activa® PC, Activa® RC and Activa® SC implantable deep brain stimulators, and RestoreUltra® and RestoreSensor® implantable spinal cord stimulators

5 Mar 2014 **Activa®, Restore®, PrimaADVANCED®, and Itrel® 4 neurostimulation devices:**
Labelling corrections to accurately account for the impact of cycling on device longevity or recharge interval

6 Mar 2014 **Medtronic Spinal Cord Stimulation (SCS) Therapy:**
Labelling update to include the potential for epidural mass causing spinal cord compression

Minocycline and risk of benign intracranial hypertension

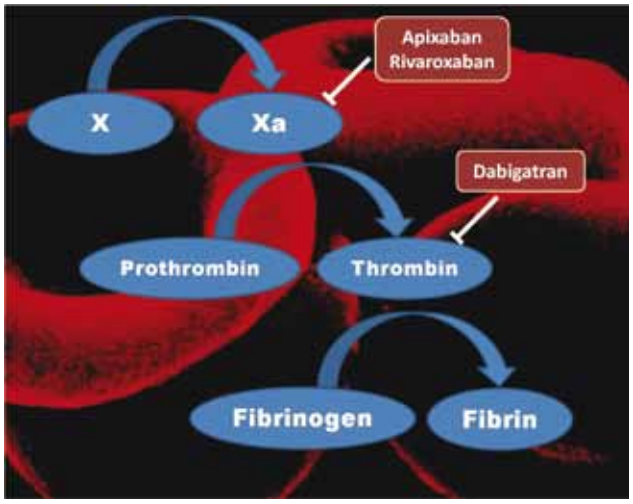
HSA has recently reviewed the safety profile of minocycline in relation to the risk of benign intracranial hypertension. Minocycline is indicated for the treatment of several infections caused by susceptible strains. It is registered locally as Apo-minocycline® (Pharmaforte Singapore Pte Ltd) and Borymycin® (Yung Shin Pharmaceutical (S) Pte Ltd) since 1998.

Benign intracranial hypertension (also known as pseudotumour cerebri) involves a persistent rise in cerebrospinal fluid pressure and is characterised by headache, nausea, vomiting and vision disturbances, including papilloedema with occasional sixth-nerve palsy. While rare, benign intracranial hypertension is known to be associated with tetracyclines, and in particular, with minocycline treatment. Concomitant use of isotretinoin (or other systemic retinoids) with minocycline should be avoided because isotretinoin is also known to be associated with benign intracranial hypertension.

The local package inserts of minocycline-containing products are being strengthened to include warnings to avoid the administration of isotretinoin or other systemic retinoids/retinol shortly before, during, and shortly after minocycline therapy. To date, HSA has not received any reports of benign intracranial hypertension associated with the use of minocycline. Healthcare professionals are recommended to take note of the above safety information and to consider the possibility of benign intracranial hypertension in patients treated with minocycline, if signs and symptoms consistent with this diagnosis are identified.

Labelling updates to mitigate the risk of bleeding with new oral anticoagulants

HSA would like to highlight recent updates made to the labelling of new oral anticoagulants (NOACs), namely the direct thrombin inhibitor dabigatran and the two direct Factor Xa inhibitors, apixaban and rivaroxaban, related to the known risk of bleeding. Dabigatran (Pradaxa®, Boehringer Ingelheim Singapore Pte Ltd), apixaban (Eliquis®, Bristol-Myers Squibb (Singapore) Pte Ltd) and rivaroxaban (Xarelto®, Bayer (South East Asia) Pte Ltd) have been registered locally since August 2009, December 2012 and November 2008, respectively.



The labelling amendments for Eliquis® were company-initiated. They include contraindication of Eliquis® in patients with a lesion or condition if considered to be a significant risk of major bleeding, as well as those receiving concomitant treatment with any other anticoagulant. HSA has reviewed these information and deemed the amendments necessary to maintain the positive benefit-risk balance of this product. In addition, HSA has assessed that the above contraindications should also be extended to Xarelto® and Pradaxa®.

Background

In 2012, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) conducted a review of available data on the risk of serious or fatal bleeding with Pradaxa®.[1] Although the CHMP concluded that the benefit-risk balance of Pradaxa® remained positive, further updates to the product information would be recommended to provide clearer guidance on how to reduce and manage the risk of bleeding. This includes identifying the types of lesions or conditions and the concomitant medications which predisposed patients to significant risk of major bleeds.

In October 2013, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) further advised that the enhanced contraindications for Pradaxa® should also extend to Eliquis® and Xarelto® for all indications and doses due to similar bleeding risks observed in clinical trials and post-marketing experience.[2]

Local situation

To date, HSA has received 25 local reports of bleeding associated with NOACs which were classified as 'serious' by the reporting doctor. The ages of the patients were provided in 19 cases, of which 84% were 60 years and over (range 37-86 years). Gastrointestinal bleeding and intracranial bleeding were reported in 56% and 16% of the cases, respectively.

HSA's advisory

HSA has reviewed the available information and assessments conducted by the EMA and UK MHRA, taking into account our local reports on serious bleeding associated with NOACs, as well as the company-initiated amendments to the Eliquis® local package insert (PI). HSA's assessment is that the local PIs of all NOACs should be strengthened to include the following shared contraindications:

- Lesion or condition at significant risk of major bleeding, such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent, such as unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.) or oral anticoagulants (warfarin, etc.), except under the circumstances of switching of therapy to or from the medicine, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

It should be noted that in addition to these shared contraindications, there are also other contraindications specific to each NOAC described in the PI for each individual drug product.

In view of the risk of haemorrhage associated with all anticoagulants, healthcare professionals are advised to take note of the indications, contraindications, posology/dosage, and warnings/precautions specific to each NOAC, as well as each individual patient's risk factors for bleeding, particularly age, weight and renal function when prescribing NOACs.

Healthcare professionals are encouraged to report any adverse reactions suspected to be related to the use of NOACs to the Vigilance Branch of HSA.

References

1 *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/05/news_detail_001518.jsp&mid=WC0b01ac058004d5c1*
2 *http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON322347*

Please send your enquiries, comments and suggestions to:

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All website references were last accessed on 28 March 2014.