HSA Health Sciences Authority

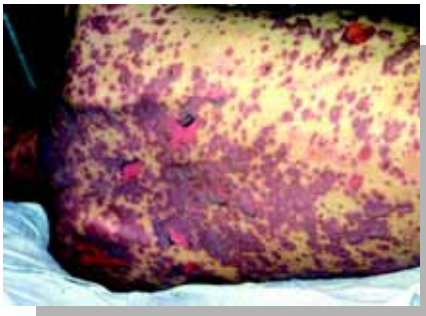
Adverse Drug Reaction news

Published by the Health Products Regulation Group, HSA and the HSA Pharmacovigilance Advisory Committee

Serious adverse skin reactions associated with carbamazepine

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening adverse skin reactions, with mortality rates of up to 5% and 40% respectively. Drugs are most often implicated as the suspected cause of SJS and TEN in adults and elderly persons.

Carbamazepine, (CBZ) indicated for the treatment of epilepsy, neuropathic pain and bipolar disorder, is known to be associated with an increased risk of causing adverse cutaneous skin reactions, including SJS and TEN. This increased risk has been observed in the local population through the relatively higher numbers of SJS and TEN that have been reported to the Health Sciences Authority (HSA) in association with the drug over the years. More recently, studies have been published which demonstrate a plausible genetic association with CBZ-induced SJS and TEN among Asian patients, in particular, Han Chinese and Thais.



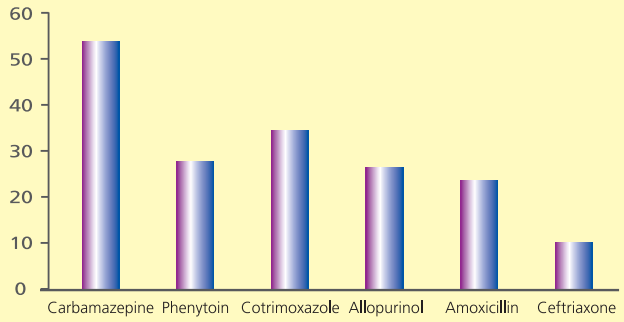
A case of Stevens-Johnson syndrome

Local ADR reports of SJS and TEN

Between 2003 and 2008, the Pharmacovigilance (PV) Branch of HSA received 290 cases of drug-induced SJS and TEN. CBZ was one of the most commonly suspected causative agents, accounting for 53 cases (18%) (in 2008 alone, 15 cases of SJS-TEN were reported in association with CBZ). These 53 reports involved patients aged one to 88 years. The CBZ dosages ranged from 100 – 600mg daily. The onset of adverse reactions ranged from one day to three months after starting therapy.

Other drugs such as allopurinol, phenytoin and cotrimoxazole were also reported to be associated with a higher number of SJS/TEN, accounting for 9.3%, 9.6% and 12.1% of the total local SJS/TEN reports received respectively (See Table 1).

Table 1. No. of cases of SJS/TEN from 2003 to 2008



Drugs more commonly reported to be associated with SJS and TEN

Association observed between the HLA-B*1502 allele and CBZ-induced SJS and TEN

Recently, CBZ-induced SJS and TEN have been found to be associated with the HLA-B*1502 allele among Han Chinese (in Taiwan and Hong Kong) and Thais.[2,3,4] In the Taiwan study, while 59 out of the 60 patients with CBZ-induced SJS/TEN had the HLA-B*1502 allele, only 4% of the CBZ-tolerant patients were found to carry the allele. Out of the 144 CBZ-tolerant patients, who had been on CBZ for at least three months and at a higher dose of CBZ, none reported any SJS nor TEN.[3]

Also, the allele HLA-B*1502 was not observed in patients with other forms of CBZ-induced cutaneous reactions such as hypersensitivity syndrome or maculopapular eruptions, suggesting that the genetic association is phenotype-specific. A case series in Hong Kong found four out of four cases of SJS/TEN to be associated with CBZ in patients positive for HLA-B*1502.[4]

A European study from the RegiSCAR group[5] found that out of the 12 patients with CBZ-induced SJS/TEN, all four who were positive for the HLA-B*1502 allele were of Asian origin. It further suggested that the genetic link may be specific to patients with Asian ancestry such as the Han Chinese.

An analysis of worldwide post-marketing cases reported to the World Health Organisation (WHO) also pointed to a much higher reporting rate of SJS/TEN, about ten times, higher in some Asian countries.[6]

Regulatory Actions taken to date

Based on the above findings and the post-marketing ADRs reported by the manufacturers of carbamazepine, the US Food and Drug Administration (FDA) concluded in December 2007, that the risk of SJS/ TEN from CBZ is significantly increased in Asian patients positive for the HLA-B*1502 allele.[6] Recognising the wide variability in rates of HLA-B*1502 even

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ISSN: 0219 - 2152
March 2009
Vol.11 No.1

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Cyproterone acetate and meningiomas

Cyproterone acetate (Androcur®, Bayer Schering Pharma and Procur®, Douglas Pharmaceuticals) is an antiandrogen that is indicated for the treatment of inoperable carcinoma of the prostate and the reduction of sexual drive in men. It is also indicated in women with severe signs of androgenization. Cyproterone acetate is available as 50mg and 100mg tablets. It is also found in smaller quantities, 2mg, in combined oral contraceptives, Estelle-35®, Diane-35® and 1mg in Climen 28®.

Meningioma Cases

Since the launch of cyproterone acetate mono-preparations in 1972, Bayer Schering Pharma® has received 24 reports (20 females, four males) of meningiomas suspected to be associated with Androcur® either used singly or in combination with estrogens. In nine of the 24 patients, multiple meningiomas were present at the time of the first meningioma diagnosis (seven females and two males). All the cases were associated with high doses of cyproterone acetate, ranging from 25mg to100mg daily and after long treatment periods of four to 24 years. Nineteen of these post-marketing cases originated from France.

Case Studies

A recently published literature abstract by Froelich et al[1] reported nine case studies of female patients, aged between 33 to 62 years old, who presented with multiple meningiomas after receiving daily cyproterone acetate treatments for durations of between ten to 20 years. The nine case studies highlighted by Froelich were not included in Bayer Schering Pharma's existing database of cases.

All 9 female patients did not present with any clinical evidence of neurofibromatosis. Dose details were available for five of the nine female patients reported in the case studies. These five female patients were on high doses of cyproterone acetate, ranging from 25 to 100mg daily taken for 11 to 21 days of the menstrual cycle. The cyproterone acetate doses were given concomitantly with transdermal/oral oestrogens for a prolonged time period, ranging from nine to 17 years.

Rapid onset of clinical symptoms was observed in six out of the nine patients, of which five of them experienced rapid decrease in visual acuity. Lesions were preferentially located at the base of the skull. Cyproterone acetate was stopped at the time of diagnosis in two of the nine patients.

Six of the nine patients were followed radiologically for a period between eight to 81 months before treatment withdrawal and significant increase in tumour size and/or the development of new lesions were observed in all the cases. A follow up of five to 32 months was initiated after treatment withdrawal and no clinical or radiological progression was observed.

Pharmacoepidemiological Study

A retrospective cohort study with nested case-control analysis will be performed by Bayer Schering Pharma® using data from The Health Improvement Network database (THIN) in the UK, to further investigate the association between cyproterone acetate and meningioma. Major study objectives will be to estimate the incidence of meningioma in the general population and among users of cyproterone acetate and to examine whether there is a dose-response relation and a duration-response relation between use of cyproterone acetate and meningioma. The study will start in 2009 and first results are expected in 2010.

Conclusion

To date, HSA has not received any local adverse drug reaction of meningiomas associated with the use of cyproterone acetate. However, healthcare professionals should take into consideration the above safety information when prescribing high dosages of cyproterone acetate to their patients. HSA will be working with the drug companies to update the prescribing information in the package inserts.

References

1. *Endocrine Abstracts (2008) 16P158*

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within ethnic groups, the difficulty in ascertaining ethnic ancestry, as well as the likelihood of mixed ancestry, FDA recommended that screening for HLA-B*1502 should be performed for most patients of Asian ancestry. Patients of any ethnicity or genotype, including HLA-B*1502 positive, who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of SJS/TEN from carbamazepine.[6]

The local package insert for Tegretol® has also been updated by the manufacturer to reflect the association observed between HLA-B*1502 allele and CBZ-induced SJS, the prevalence of this allele in vaious Asian population as well as a recommendation to consider testing for the presence of HLA-B*1502 allele in patients with Asian ancestry prior to prescribing Tegretol®. In addition, it is also stated that the use of carbamazepine should be avoided in patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. However, it is not known if a patient who tests positive for HLA-B*1502 would develop SJS/TEN when alternative anti-epileptics are used.

Currently, the HSA's Tissue Typing Laboratory (Tel: 62130632, 62130633) is the only accredited lab in Singapore that offers HLA testing as part of their diagnostic services. Prescribers may send their patients' samples for a preliminary test to check for the presence of the HLA-B15 serotype (HLA-B Low Resolution), and then proceed to test for the presence of the HLA-B*1502 allele (HLA-B High Resolution) if the former is positive. Alternatively, prescribers could also proceed directly to test for the presence of the HLA-B*1502 allele. The turnaround time is estimated to be between three to seven working days.

Pharmacogenetics initiative by HSA

In an effort to understand the relevance of genetic association with adverse drug reactions among the diverse ethnic groups (Chinese, Malays and Indians) in the local population, HSA is embarking on a pharmacogenetics-based pharmacovigilance programme together with scientific collaborators from the various public institution hospitals and research institutes. The study is aimed at investigating the significance of the genetic association of the HLA-B*1502 allele to CBZ-induced serious skin reactions in the local context and also to uncover other possible genetic associations that may be responsible for the adverse drug-induced skin reactions observed locally.

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Codeine toxicity in breastfed infants

Use of codeine by some nursing mothers may lead to life-threatening adverse effects in breastfed infants

HSA would like to bring the attention of healthcare professionals to a very rare, but serious health risk in breastfed infants posed by codeine use in nursing mothers who are ultra-rapid metabolisers of codeine.

Background

Codeine is found in many prescription and non-prescription pain relievers and cough syrups. Once ingested, codeine is metabolised by cytochrome P450 2D6 (CYP2D6) to its active metabolite, morphine, which relieves pain or cough. Limited evidence suggests that individuals with a specific CYP2D6 genotype or otherwise known as ultra-rapid metabolisers, may convert codeine to morphine more rapidly and completely than other people. In nursing mothers, this metabolism can result in a higher than expected levels of morphine in serum and breast milk, putting nursing infants at increased risk for morphine overdose.[1]

Prevalence of ultra-rapid metabolisers in different ethnic groups

The frequency of CYP2D6 genotype associated ultra-rapid metabolisers varies widely among different racial and ethnic groups. The prevalence is estimated to be 1 per 100 people for those of Chinese, Japanese and Hispanic descent, 3 per 100 for African Americans and 1 to 10 per 100 for Caucasians. North African, Ethiopian and Arab populations have the highest estimated prevalence, from 16 to 28 per 100 people. Regardless of ethnic variation in the prevalence of ultra-rapid metabolisers, it is important to bear in mind that polymorphism of CYP2D6 is clinically important.

Case report in the Lancet[2]

In August 2006, the Lancet published a case report describing a healthy 13-day-old nursing infant who died from morphine overdose. The mother was prescribed 60mg of codeine every 12 hourly after birth for episiotomy pain. This dose was subsequently reduced to 30mg every 12 hourly after she developed side effects of somnolence and constipation. The breastfed infant was found to have poor neonatal feeding around postpartum day ten, noted to have grey skin on day 12 and died on day 13. Postmortem analysis showed no anatomical anomalies but the infant's morphine blood concentration was found to be 70ng/ml.

Serum morphine concentrations of breastfed neonates of nursing mothers who are taking codeine typically range from 0 to 2.2ng/ml. A sample of breast milk that was stored on day 10 showed a morphine concentration of 87ng/ml, which was much higher than the typical range of morphine milk concentrations of 1.9 to 20.5ng/ml at repeated codeine doses of 60mg every 6 hours.

Subsequent genotypic analysis of the mother revealed that she was heterozygous for the CYP2D6*2A allele with CYP2D6*2x2 gene duplication which classified her as an ultra-rapid metaboliser. Additionally, genotypic analyses of the maternal grandfather, the father, and the infant showed that they were extensive metabolisers while the maternal grandmother was an ultra-rapid metaboliser.

International regulatory actions

In August 2007, the United States Food and Drug Administration (FDA) issued a public health advisory to warn healthcare professionals and nursing mothers of the increased risk of morphine overdose in breastfed infants of mothers who are taking codeine and are ultra-rapid metabolisers. According to the FDA, nursing mothers have used codeine safely for many years and in medical practice, codeine is generally considered the safest choice among narcotic pain relievers for nursing women and their babies. However, to raise awareness of this potential health risk and to prevent morphine overdose in breastfed infants, FDA is requiring manufacturers of prescription codeine medicines to update their product inserts to include information about codeine ultra-rapid metabolism.[3,4]

A similar public advisory was also issued recently by Health Canada in October 2008. Nursing mothers were advised to take precautions to minimise the risk of morphine exposure in breastfed infants and to monitor their infants carefully when they are taking codeine-containing products during breastfeeding. Drug manufacturers of codeine-containing prescription products were also requested to update their product inserts to include information that better identify the risk to breastfed infants whose mothers are ultra-rapid metabolisers of codeine. The labelling guidelines for non-prescription products containing codeine were also being revised to provide more information about this risk.[5]

Local situation

HSA has not received any local reports related to toxic morphine levels in breastfed infants as a result of codeine-containing products ingested by nursing mothers.

When prescribing codeine to a nursing mother, physicians should choose the lowest effective dose for the shortest period of time. Healthcare professionals are encouraged to report suspected adverse drug reactions associated with codeine-containing products to the Pharmacovigilance Branch of HSA.

References

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2. *Lancet 2006, Vol 368:704, August 2006*
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4. *FDA News. FDA warning on codeine use by nursing mothers. http://www.fda.gov/bbs/topics/NEWS/2007/NEW01685.html*
5. *Health Canada Advisory. Use of Codeine Products by nursing mothers. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_164-eng.php*

Analysis of 2008 ADR Reports

The Pharmacovigilance Branch of HSA administers the national adverse drug reaction (ADR) monitoring programme. It is an important post-marketing surveillance tool which enables the early detection of local drug safety signals.

In the year 2008, a total of 9,107* adverse event reports were received by the Pharmacovigilance Branch, HSA. Of these cases, 3,155 reports were reviewed and captured in the national database.

Majority of the reports reviewed were associated with pharmaceutical products (89.1%), followed by complementary medicines (8.6%), vaccines/biologics (1.1%) and others which include health supplements and cosmetics.

Source of ADR reports (n= 3,155)

The reports were submitted by healthcare professionals working in the public hospitals (47.9%), government clinics (43.3%), pharmaceutical companies (4.3%), private clinics/hospitals (3.8%) and community pharmacies (0.7%).

Review of ADR reports

With regard to the profile of patients, there were more reports received in females than males and the ratio of male to female is 1 : 1.2.

The top ten suspected drugs commonly reported to cause ADRs are listed in Table 1. Most of the ADRs reported, classified according to system-organ class were skin-related disorders (22.4%), followed by body as a whole (general disorders) (14.7%), and nervous system (11.3%). See Table 2 for more information.

Serious ADR reports

Serious ADR reports made up 49% of the total reports reviewed. Among these were 21 fatal reports, ten of which were suspected to be linked to the consumption of illegal sexual enhancement products, namely Power 1 Walnut (动力一号核桃素片), fake Cialis and Zhong Hua Niu Bian (中華牛鞭). Most of the other fatal reports (eight) were assessed to have multiple confounding factors such as concomitant medical conditions or not directly contributed by the drug. Some examples of serious ADR reports are listed in Table 3.

ADR reports associated with complementary medicines

Nine percent (270) of total reports received were associated with complementary medicines. Illegal sexual enhancement products made up the majority of these reports (240 reports). Of the remaining 30 reports associated with traditional medicines and Chinese Proprietary Medicines, 86% were serious. The ADRs reported were mainly associated with hepatic dysfunctions (13), followed by skin eruptions (6) and endocrine disorders (6) such as hypoadrenalism, and thyrotoxicosis. The rest were associated with renal, blood and gastrointestinal disorders. Laboratory tests were conducted on the suspected products when there was a high suspicion of adulteration with common poisons. Some of the detected adulterants include sibutramine, piroxicam, chlorpheniramine, hydrochlorothiazide and prednisolone.

Table 1: Top 10 suspected drugs (by active ingredients) commonly reported to cause ADRs

Top	Active Ingredients	No. of reports**
1	Atenolol	157
2	Hydrochlorothiazide	116
3	Simvastatin	108
4	Diclofenac	106
5	Metoclopramide	83
6	Coamoxiclav	79
7	Enalapril	77
8	Paracetamol	74
9	Docetaxel	73
10	Cotrimoxazole	65

*** More than one suspected drug may be implicated in an ADR report.*

Table 2: Top 10 ADRs by system-organ classes

Top	System organ class^	No. of reports (%#)
1	Skin & Appendages	1,193 (22.4)
2	Body as a whole	782 (14.7)
3	Nervous	603 (11.3)
4	Respiratory	463 (8.7)
5	Gastro-Intestinal	442 (8.3)
6	Metabolic & nutritional	426 (8.0)
7	Psychiatric	246 (4.6)
8	Cardiac	207 (3.9)
9	Vascular (extracardiac)	166 (3.1)
10	Musculoskeletal	164 (3.1)

^ *The system-organ class refers to the adverse reaction terminology developed by the WHO.*

\# *Percentage of total no. of ADR terms quoted (n= 4,692)*

Conclusions

The national ADR monitoring programme relies primarily on the spontaneous ADR reports submitted by healthcare professionals to enable HSA to detect potential drug safety signals. HSA encourages all healthcare professionals to report your suspicions of adverse event linked to usage of western medicines, vaccines and complementary health products including herbal and traditional medicines. You do not need to be certain of the causality link between the adverse event and the product, a suspicion of the association would suffice to submit a report to the Pharmacovigilance Branch of HSA.

The ADR reports received by HSA are also submitted to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring at Uppsala, Sweden for collation of ADR data on a global level, contributing to the international pharmacovigilance effort.

* *Not all reports that were submitted electronically to HSA via the Critical Medical Information Store (CMIS) were included for review as many comprised non-serious reactions or lacked details such as the ADR description and the suspected drug.*

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Table 3: Drugs suspected of causing serious blood, hepatic and skin adverse reactions

Description	WHO ADR preferred term	Suspected drug (number in bracket represents number of times the drug has been implicated+)
Blood disorders	Agranulocytosis, neutropenia	aspirin (1), alemtuzumab (1), benzylpenicillin (1), complementary medicine (1), carbamazepine (1), ciclosporin (1), clozapine (2), deferasirox (1), fludarabine (1), imatinib (1), nevirapine (1), piperacillin and tazobactam (2), propylthiouracil (1), ticlopidine (1)
	Leucopenia	amoxicillin (1), ceftriaxone (1), cloxacillin (1), clozapine (3), cotrimoxazole (1), deferasirox (1), mefenamic acid (1), piperacillin and tazobactam (1), sulfasalazine (1), ticlopidine (2)
	Pancytopenia	azathioprine (2), carbamazepine (1), deferasirox (1), fusidic acid (1), complementary medicine (1), methotrexate (1), phenytoin (1), teicoplanin (1), vancomycin (1)
	Thrombocytopenia	allopurinol (1), azathioprine (1), carbamazepine (2), cefuroxime (1), ceftazidime (1), cotrimoxazole (1), etoricoxib (1), imatinib (1), imipenem and cilastatin (1), methotrexate (1), piperacillin (1), rifampicin (1), sulfasalazine (1), ticlopidine (1), vancomycin (1)
Hepatic disorders	Cholestatic hepatitis	ciprofloxacin (2), frusemide (1), complementary medicines (2), mirtazapine (1), phenytoin (1), piperacillin and tazobactam (1), simvastatin (1), ticlopidine (2)
	Hepatitis, Hepatitis with jaundice	allopurinol (1), amoxicillin (1), atorvastatin (1), azathioprine (2), cotrimoxazole (3), complementary medicines (10), chlorpromazine (1), dapsone (1), diclofenac (1), erythromycin (1), esomeprazole (1), etoricoxib (1), ezetimibe (1), fenofibrate (1), isoniazid (1), isotretinoin (1), lamotrigine (1), phenytoin (1), rifampicin (1), terbinafine (1)
Skin Disorders	Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), SJS-TEN	allopurinol (5), amoxicillin (3), carbamazepine (15), cefalexin (1), cefazolin (1), ceftriaxone (1), ciprofloxacin (1), clarithromycin (2), clindamycin (1), cloxacillin (1), coamoxiclav (4), cotrimoxazole (4), dapsone (2), doxycycline (2), enalapril (1), esomeprazole (1), ethambutol (1), etoricoxib (3), fluconazole (1), ganciclovir (1), ginkgo biloba (1), imipenem and cilastatin (2), isoniazid (1), levofloxacin (1), mefenamic acid (1), meropenem (1), omeprazole (2), paracetamol (1), phenytoin (2), piperacillin and tazobactam (3), piroxicam (1), propranolol (1), pyridoxine (1), simvastatin (1), strontium ranelate (1), valproic acid (1), vancomycin (1)

+ More than one suspected drug may be implicated in a single ADR report.

A REMINDER TO UPDATE YOUR PARTICULARS AT THE MOH HEALTH PROFESSIONAL PORTAL (HPP)

Healthcare professionals can receive important time-sensitive information hosted on the Health Professional Portal (HPP) via email and SMSes.

These information are conveyed through 3 channels, namely MOH MedAlert, HSA Drug Safety and MedInfo which carry different types of health-related information:

- MOH MedAlert – Alert from MOH on latest trends and developments of disease outbreaks in Singapore e.g. SARS and Chikungunya.
- HSA Drug Alert – Alert from HSA on major drug issues, product recalls and withdrawals pertaining to medicinal and health products available locally
- MedInfo – Guidance from MOH to doctors on specific practice-related issues e.g. update on melamine-contaminated powdered infant formula and request for increase vigilance

In order to receive these important health information in a timely manner, healthcare professionals are urged to update your profile, namely your email address and contact number* in HPP.

How to update your profile

It takes only a few steps to access HPP to update your contact details: log into HPP at http://www.hpp.moh.gov.sg. Click under the professional group that you belong to, e.g. doctors, pharmacists or dentists. Login your professional registration number or Singpass and this will bring you to the secured health professional website. Update your contact details by clicking the "My Profile" icon (located on top left hand corner of the page). If you have any queries, please contact the MOH HPP Helpdesk at (65) 6325 9491 or (65) 6325 2953 or email: moh_hpp_helpdesk@moh.gov.sg.

* *Postal addresses have to be updated with your respective professional boards.*

Moxifloxacin (Avelox®): A Safety Update

Risk of liver injuries and bullous skin reactions

Moxifloxacin (Avelox®, Bayer HealthCare and Vigamox®, Alcon) is a broad-spectrum antibacterial that is available locally in the form of an oral tablet, infusion solution and ophthalmic solution. Avelox® tablet and infusion solution have been registered in Singapore since July 2000 and May 2002 respectively while Vigamox® ophthalmic solution was licensed in November 2004.

Recent safety concerns

In February 2008, Bayer HealthCare issued a Dear Healthcare Professional Letter (DHCPL) in Europe to inform healthcare professionals of very rare liver injuries and serious skin reactions associated with moxifloxacin. This was in response to a worldwide review of serious, including fatal cases of hepatotoxicity and bullous skin reactions such as Stevens-Johnson-syndrome (SJS) and toxic epidermal necrolysis (TEN) reported for moxifloxacin. In this review, there were eight reports of fatal hepatic injuries considered as possibly related to moxifloxacin therapy. Thirty-five cases of SJS were reported, of which, three had fatal outcomes and seven were considered life threatening. TEN was reported in several cases where a causal relationship was considered possible. Healthcare professionals were reminded that moxifloxacin is contraindicated in patients with impaired liver function (Child Pugh C) and in patients with transaminases elevations greater than 5-fold the upper limit normal (ULN).

In July 2008, the European Medicines Agency (EMEA) finalised their safety review of oral moxifloxacin-containing medicines. The review concluded that the benefits of oral moxifloxacin-containing medicines continue to outweigh the risks. However, in view of the increased risk of adverse hepatic reactions associated with moxifloxacin, it was recommended to restrict oral moxifloxacin-containing medicines to second-line therapy in the EMEA approved indications of treatment of acute bacterial sinusitis, acute exacerbations of chronic bronchitis and community-acquired pneumonia. In addition, the warnings concerning the risk of diarrhoea, heart failure in women and older patients, severe skin reactions and fatal liver injuries were also strengthened in the products' labelling.

Local situation

To date, HSA has received 22 local spontaneous adverse drug reaction reports associated with moxifloxacin. Patient exposure to moxifloxacin to date is estimated to be 230,577*, according to local figures provided by Bayer Healthcare. In the interpretation of the above figures, there is a need to consider the significant degree of under-reporting of adverse reactions as is the case with all spontaneous adverse drug reaction reporting programmes.

A majority of these reports were concerning skin reactions, of which there was one report of SJS, one report of urticaria, four reports of rashes, two reports of anaphylaxis and five reports of anaphylactic shock. In addition, there were two reports of hepatobiliary disorders, of which one of the patient developed jaundice on the ninth day of moxifloxacin therapy while the other developed elevated liver enzymes.

Moxifloxacin is indicated locally for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, and uncomplicated skin and skin structure infections. These indications are similar to those approved by the US Food and Drug Administration (FDA).

The package inserts for moxifloxacin tablets and infusion solution will be updated with safety information on fulminant hepatic failure and bullous skin reactions, in addition to the existing warnings on anaphylactic reaction and abnormal liver function. Although moxifloxacin-containing products are not restricted to second-line therapy locally, physicians are advised to be aware of the development in Europe. Physicians are also advised to be vigilant for early signs and symptoms of severe liver injury and bullous skin reactions such as SJS or TEN in patients taking moxifloxacin.

Healthcare professionals are encouraged to report suspected adverse drug reactions associated with moxifloxacin to the Pharmacovigilance Branch of HSA.

* *For tablets, patient exposure is estimated on a defined daily dose[3] (DDD) of moxifloxacin of 400mg and assuming an average 7-day treatment course per patient. For injections, patient exposure is estimated on a DDD of 400mg and assuming an average 4-day treatment course per patient.*

References

1. *EMEA Press Release: European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines. http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf*
2. *Direct Healthcare Professional Communication regarding moxifloxacin (Avelox®) and serious hepatic and bullous skin reactions. http://www.mhra.gov.uk/homeidcplg?IdcService=GET_FILE&dDocName=CON014103&RevisionSelectionMethod=Latest*
3. *WHO Collaborating Center for Drug Statistics Methodology (Oslo).*

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from September 2008 to December 2008. Please note that due to space constraints, the list published is not exhaustive and you are encouraged to refer to the following website for the complete listing with details: http://www.hsa.gov.sg/safetyinfo_and_recalls. Please also note that there might be some lag time in the availability of the package insert which reflects the latest change(s).

1. Alendronate (Fosamax®, MSD) Precautions: Low-energy fractures (stress fractures or insufficiency fractures in absence of trauma) of subtrochanteric & proximal femoral shaft reported in bisphosphonate-treated patients. Possible prodromal pain in affected area, often associated with imaging features of stress fracture, weeks to months before complete fracture occurred. Evaluate patients with suspected stress fractures for known causes & risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use). New ADRs: Osteomyelitis, low-energy femoral shaft fracture, alopecia.

2. Alfuzosin (Xatral® SR & XL, Sanofi-Aventis) Special warning: Intraoperative Floppy Iris Syndrome (small pupil syndrome variant) observed during cataract surgery in patients previously or currently treated with tamsulosin. Isolated cases also reported with other alpha-1 blockers. New ADRs: Nasal congestion, urticaria, angioedema.

3. Alteplase & tenecteplase (Actilyse® & Metalyse®, Boehringer Ingelheim) Contraindications: Haemorrhagic stroke or stroke of unknown origin at any time; ischaemic stroke or transient ischaemic attack (TIA) in the preceeding 6 months. Special precaution: Concomitant use of GPIIb/IIIa antagonists increases risk of bleeding. Side effects: Life-threatening haemorrhage can occur. Reperfusion arrhythmias (e.g. arrhythmia, extrasystoles) occur in close temporal relationship to treatment & may lead to cardiac arrest, can be life threatening & may require use of conventional antiarrhythmic therapies. New ADRs: Cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage, eye haemorrhage, gastric haemorrhage, retroperitoneal haematoma, haematuria, urinary tract haemorrhage.

4. Anastrozole (Arimidex®, AstraZeneca) New ADRs: Carpal Tunnel Syndrome, hepatitis, increase in the following: alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-GT & bilirubin.

5. Aprepitant (Emend®, MSD) Precaution: Emend® affects the pharmacokinetics of orally administered CYP3A4 substrates more than intravenously administered CYP3A4 substrates. Side effects: For prevention of post-operative nausea & vomiting in non-chemotherapy patients receiving general balanced anaesthesia, ADRs observed at greater incidence than with ondansetron included increased ALT, upper abdominal pain, abnormal bowel sounds, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, reduced visual acuity, wheezing. Serious ADRs reported in PONV studies in patients on higher dose of aprepitant: Constipation & sub-ileus. New ADR: Anaphylactic reactions.

6. Aripiprazole (Abilify®, Bristol-Myers Squibb) New ADRs: Dystonia, diarrhoea. Symptoms of dystonia may occur during 1st few days of treatment. Can occur at low doses, & occur more frequently & with greater severity with high potency & at higher doses of 1st generation antipsychotics. Elevated risk of acute dystonia observed in males & younger age groups.

7. Atazanavir (Reyataz®, Bristol-Myers Squibb) Precaution: Nephrolithiasis reported post-market in HIV-infected patients. New ADRs: Oedema, 2° AV block, pancreatitis, hepatic function abnormalities, hyperglycaemia, diabetes mellitus, arthralgia, nephrolithiasis, pruritus, alopecia, maculopapular rash.

8. Bisacodyl (Dulcolax®, Boehringer Ingelheim) Pregnancy: Use with caution during 1st trimester.

9. Bortezomib (Velcade®, J&J) New ADR: Septic shock.

10. Ceftriaxone (Rocephin®, Roche) Contraindication: Must not be administered with calcium-containing solutions in newborns due to risk of ceftriaxone-calcium salt precipitation. Fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in newborns. Rocephin® or ceftriaxone & calcium-containing solutions must not be mixed or administered within 48 hours of each other in any patient, even via different infusion lines.

11. Ciclosporin (Sandimmun®, Novartis) Special warnings: Avoid excess UV light exposure due to risk of skin malignancy. Monitor renal function in elderly patients. Caution while co-administering lercanidipine with ciclosporin. Limited experience with use in endogenous uveitis in children. Interactions: Oxcarbazepine, bosentan, voriconazole, colchicine, nefazodone, etoposide, methotrexate, repaglinide, K+ sparing drugs or K+ containing drugs. Ciclosporin, a CYP3A4 & multidrug efflux transporter P-glycoprotein inhibitor, may increase plasma levels of co-medications. Undesirable effects: Increased risk of potentially fatal viral, bacterial, fungal, parasitic infection, increased risk of lymphomas or lymphoproliferative disorders & skin malignancies. Frequency of malignancies increases with intensity & duration of therapy & may be fatal. Pregnancy: Pregnant women receiving immunosuppressive therapies after transplant are at risk of premature delivery (< 37 weeks).

12. Ciprofloxacin (Ciprobay®, Bayer) Special warnings: Caution in patients with history of tendon disorders related to quinolone treatment. Patients at risk of tendonitis & tendon rupture include the elderly, kidney, heart, & lung transplant recipients & patients on concomitant steroid therapy. New ADR: Mycotic superinfection.

13. Entacapone (Comtan®, Novartis) Special warnings: Patients who experience progressive anorexia, asthenia & weight decrease within a relatively short period of time should have a general medical evaluation including liver function. Pathological gambling, increased libido & hypersexuality reported in Parkinson's disease patients treated with dopamine agonists and combination of entacapone & levodopa. New ADRs: Skin, hair, beard & nail discolourations.

14. Ertapenem (Invanz®, MSD) New ADR: Altered mental status.

15. Everolimus (Certican®, Novartis) Special warning: Patients are at increased risk of developing infections esp. infections with opportunistic pathogens. New ADRs: Pericardial & pleural effusion.

16. Exemestane (Aromasin®, Pfizer) New ADR: Cholestatic hepatitis.

17. Fludarabine (Fludara®, Bayer Schering) Contraindication: CrCL < 30 ml/min. Special warnings: Trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia & death reported in previously treated or untreated adult patients. Duration of clinically significant cytopenia: ~ 2 months to 1 year. Disease progression and transformation (e.g. Richter's Syndrome) commonly reported in CLL patients. Careful monitoring for haematological toxicity required. Possible dose reductions in patients with renal impairment, depressed white cell or platelet count & patients with infection or bleeding. New ADRs: Autoimmune haemolytic anaemia, thrombocytopenic purpura, pemphigus, Evan's syndrome, acquired haemophilia, anorexia, mucositis, abnormal hepatic enzyme. Pregnancy: Use in early pregnancy resulting in pregnancy loss (in Fludara® monotherapy & combination therapy) and skeletal & cardiac malformation have been reported. Premature delivery reported.

18. Formoterol (Foradil®, Novartis) Special warning: Upon controlling asthma symptoms, reduce dose gradually with regular monitoring. Use lowest effective dose. New ADRs: Bronchospasm paradoxical, hypokalaemia, hyperglycaemia, prolonged QT.

19. Hydroxychloroquine (Plaquenil®, Sanofi-Aventis) Special warnings: Opthalmological examination (including fundoscopy & colour vision) if cumulative dose is > 200g. Stop drug immediately if abnormal colour vision noted. Patients on long-term therapy to undergo periodic examination of skeletal muscle function & tendon reflexes & withdraw drug if weakness occurs. Interaction: Hydroxychloroquine may enhance effects of hypoglycaemic treatment-to decrease doses of insulin or antidiabetic drugs.

New ADRs: Scotomatous vision with paracentral (pericentral rign types, temporal scotomas & abnormal colour vision), erythema multiforme, SJS, photosensitivity, fever, hyperleukocytosis, hearing loss, skeletal muscle myopathy or neuromyopathy, progressive weakness & atrophy of proximal muscle groups, depression of tendon reflexes, abnormal nerve conduction, anaemia, aplastic anaemia, agranulocytosis, decrease in WBCs, thrombocytopenia, bronchospasm. Pregnancy: Should not be used in pregnancy.

20. Imipenem, cilastatin (Tienam®, MSD) Interaction: Carbapenem antibiotics reported to decrease serum levels of valproic acid & breakthrough seizures have occurred in some cases.

21. Immune globulin (Gammagard S/D®, Baxter Healthcare) Posology: Patients who have underlying renal disease or who are judged to be at risk of developing thrombotic events should not be infused rapidly with any IVIG product.

22. Leflunomide (Arava®, Sanofi-Aventis) Contraindication: Hypersensitivity to active substance (esp. previous Stevens Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme). New ADRs: Renal failure, increased CPK, increased lactate dehydrogenase, hypouricaemia, hypophosphataemia.

23. Miconazole, hydrocortisone (Daktacort®, J&J) Interactions: oral anticoagulants, oral hypoglycaemics & phenytoin. Serum concentrations of hydrocortisone may be higher when using Daktacort® compared with topical preparations containing hydrocortisone alone. New ADRs: Anaphylactic reaction, contact dermatitis, erythema, rash.

24. Omeprazole (Omezol®, Hospira) Interactions: Diazepam, phenytoin & warfarin. Absorption of drugs (eg. ketoconazole) may be altered due to decreased intra-gastric acidity during omeprazole treatment. New ADRs: Photosensitivity, bullous eruption, erythema multiforme, SJS, toxic epidermal necrolysis, alopecia, stomatitis, candidiasis, paraesthesia, feeling faint, mental confusion, agitation, depression, hallucinations, arthritic & myalgic symptoms, aggression, gynaecomastia, impotence, leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, anaphylactic shock, bronchospasm, encephalopathy, hepatitis with or without jaundice, hepatic failure, interstitial nephritis leading to ARF, irreversible visual impairment.

25. Recombinant human interferon gamma-1b (Imukin®, Boehringer Ingelheim) Special precautions: Patients with pre-existing cardiac disease may experience an acute, self-limited exacerbation of cardiac condition at doses of 250mcg/m2/day or higher. Reversible, severe & possibly dose-related neutropenia & thrombocytopenia observed during therapy. Caution in patients with myelosuppression & hepatic insufficiency. Elevations of AST &/or ALT observed 7 days after starting therapy. Incidence appeared to be higher in patients < 1 year old. Drugs with myelosuppressive effects may increase toxicity of interferons. New ADRs: Flu-like symptoms, depression, back pain, abdominal pain, proteinuria, positive autoantibody, SLE, hyponaetraemia, hyperglycaemia, hypertriglyceridaemia, confusional state, disorientation, gait disturbance, Parkinsonian gait & tremor, convulsion, hallucinations, tachyarrhythmia, AV block, cardiac failure, myocardial infarction, hypotension, syncope, TIA, DVT, pulmonary embolism, tachypnoea, bronchospasm, GI haemorrhage, pancreatitis, hepatic failure, exacerbation of dermatomyositis, reversible renal failure.

26. Somatostatin (Somatostatin-ucb®, UCB) Contraindications: Known hypersensitivity to somatostatin or somatostatin analogues. Warnings & precautions: Somatostatin-ucb® intended for hospital use. To halve dose in patients with severe renal failure (CrCL < 30 ml/min). At the beginning of infusion, hypoglycaemia may occur, possibly followed 2 to 3 hours later by rise in blood sugar. Precaution: Simultaneous administration of any form of sugar (glucose, fructose or TPN). Somatostatin may induce transient systemic hypertension, transiently reduced cardiac output, increased pulmonary arterial pressure, increased central venous pressure, systemic hypotension, bradycardia, atrioventricular block. Monitor patient's vital signs during initial phase of administration, esp. after bolus injection. Caution in patients with compromised cardiovascular status or history of cardiac arrhythmia. Check renal function & plasma electrolytes regularly. Somatostatin-ucb® causes inhibition of intestinal absorption of certain nutriments & other GI hormone secretions. Abrupt interruption of infusion may result in rebound effect, esp. in patients treated for fistulae. Interactions observed with drugs that influence blood glucose regulation, plasma renin level, & arterial BP. New ADRs: AV block, bradycardia, arrhythmia, ventricular extrasystole, hyperglycaemia, hypoglycaemia, hypertension, hypotension. Not to be used during lactation.

27. Topiramate (Topamax®, J&J) ADRs: Calcinosis, apraxia, aura, complex partial seizure, pancreatitis.

28. Verteporfin (Visudyne®, Novartis) New ADR: Retinal pigment epithelial tear. Lactation: Postpone treatment or interrupt breastfeeding for at least 48 hours following dosing.

Continuing Education Point accreditation of the HSA ADR News Bulletin

Doctors and dentists can now claim one non-core Continuing Medical Education (CME) or Continuing Professional Education (CPE) point respectively under category 3A for reading each issue of the HSA ADR News Bulletin. Each issue of the bulletin is valid for two years.

With the addition of CME and CPE (dental) accreditation, the HSA ADR News Bulletin is now accredited by three healthcare professional boards namely the Singapore Medical Council, the Singapore Dental Council and the Singapore Pharmacy Council. All healthcare professionals can access the HSA ADR News Bulletin online via the Ministry of Health's Health Professional Portal (http://www.moh.hpp.gov.sg) or the HSA website (http://www.hsa.gov.sg/safetyinfo_and_recalls).

Sales of efalizumab (Raptiva®) suspended

HSA concludes that risks of efalizumab outweighs its benefits

The Health Sciences Authority (HSA) has requested Merck Pte Ltd to suspend the sales of efalizumab (Raptiva®) in Singapore with effect from 26 February 2009 due to the emergence of new safety issues associated with the product.

Raptiva® is available locally as a prescription medicine. It contains the active ingredient, efalizumab, an immunomodulating, humanized monoclonal antibody, licensed for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates of phototherapy or systemic therapy.

Risk-benefit assessment of Raptiva®

HSA and its Pharmacovigilance Advisory Committee have assessed the relevant data available to date which included the recent adverse reports of Progressive Multifocal Leukoencephalopathy (PML) and the limited place in therapy of Raptiva® in the local setting and concluded that the risk versus benefit of Raptiva® is no longer favourable. The review took into consideration the risks of the rare but potentially fatal PML associated with Raptiva®, the fact that it is not a first-line therapy, that it is used in a potentially serious but non-life threatening condition, and the availability of other treatment options for plague psoriasis. Besides PML, Raptiva® is also associated with serious adverse effects such as Guillain-Barre and Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections.

PML is a rare neuromuscular disease caused by opportunistic infections that usually leads to severe disability or death. There is no reliable way of knowing which patients will develop PML or when the disease is likely to occur. To date, there are four worldwide reports of PML (three virologically confirmed and one suspected) associated with the product in patients who had been continuously treated with Raptiva® for three or more years. Two of the three confirmed cases resulted in the patient's death. Locally, the HSA has not received any adverse drug reaction reports associated with Raptiva®.

Regulatory actions taken by international agencies

The sale of Raptiva® has been recently suspended in Europe and Canada by the European Medicines Agency (EMEA) and Health Canada respectively. Both agencies have also considered the risk-benefit profile of Raptiva® to be unfavourable.

The US Food and Drug Administration (US FDA) is currently reviewing the latest information about Raptiva® and has committed to take appropriate steps to ensure that the risks of Raptiva® do not outweigh its benefits. In October 2008, the US product labeling for Raptiva® was revised to highlight in a boxed warning the risks of life-threatening infections, including PML. A risk evaluation and mitigation strategy (REMS) to include a medication guide to educate patients about the drug's risks was also developed.

HSA's advisory

In the light of this safety issue, healthcare professionals are advised not to start new patients on Raptiva®. Those patients currently taking the drug should however, not have their therapy discontinued abruptly. Instead, healthcare professionals are advised to review the treatment of patients currently taking this drug to assess the most appropriate alternatives as soon as possible.

They should also monitor their patients who have been treated with Raptiva® closely for neurological symptoms and symptoms of infection. The effects of Raptiva® on the immune system may last for about eight to 12 weeks.

References

1. *EMEA Press Release. http://www.emea.europa.eu/humandocs/PDFs/EPAR/raptiva 2085709en.pdf*
2. *EMEA Questions and Answers on Raptiva®. http://www.emea.europa.eu/humandocs/PDFs/EPAR/raptiva/ RaptivaQ&A_1552509en.pdf*
3. *Health Canada's healthcare professional communication. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ raptiva_2_hpc-cps-eng.pdf*

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