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.

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).

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 group5 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 continued on page 2
Cyproterone acetate and meningiomas

Cyproterone acetate (Androcur®, Bayer Schering Pharma AG. 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. reported nine case studies of female patients, aged between 33 to 62 years old, who were 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.

Pharmacopoenidological 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


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.

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 various Asian populations 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-B*1502 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.

References

2. Epilepsia 2008, 49(12):2087-2091
5. Pharmacogenomics J. 2006, 6(4), 265-268

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 preceded by the initial concentration of 70ng/ml. However, the infant’s morphine blood analysis showed no anatomical anomalies and died on day 13. Postmortem investigation revealed grey skin on day ten, noted to have grey skin on day 12. Subsequent genotypic analysis of the mother revealed that she was heterozygous for the CYP2D6*2 allele with CYP2D6*2x2 gene duplication which classified her as an ultra-rapid metaboliser. Additionally, genotypic analysis of the maternal grandfather, the father, and the infant showed that they were extensive metabolisers while the maternal grandmother was an ultrarapid 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.3

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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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 (4.3%), private clinics/hospitals (3.8%) and community pharmacies (0.7%).

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 (power 1 瘦身腰豆), 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

<table>
<thead>
<tr>
<th>Top</th>
<th>Active Ingredients</th>
<th>No. of reports**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atenolol</td>
<td>157</td>
</tr>
<tr>
<td>2</td>
<td>Hydrochlorothiazide</td>
<td>116</td>
</tr>
<tr>
<td>3</td>
<td>Simvastatin</td>
<td>108</td>
</tr>
<tr>
<td>4</td>
<td>Diclofenac</td>
<td>106</td>
</tr>
<tr>
<td>5</td>
<td>Metoclopramide</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>Coamoxiclav</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>Enalapril</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>Paracetamol</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>Docoprostol</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>Cotrimoxazole</td>
<td>65</td>
</tr>
</tbody>
</table>

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

Table 2: Top 10 ADRs by system-organ classes

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

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

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.

† DOCTORS, DENTISTS & PHARMACISTS CAN NOW CLAIM CONTINUING EDUCATION POINTS FOR READING THE HSA ADR NEWS BULLETIN
### Table 3: Drugs suspected of causing serious blood, hepatic and skin adverse reactions

<table>
<thead>
<tr>
<th>Description</th>
<th>WHO ADR preferred term</th>
<th>Suspected drug (number in bracket represents number of times the drug has been implicated*)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agranulocytosis, neutropenia</td>
<td>aspirin (1), almtuzumab (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)</td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>amoxicillin (1), ceftriaxone (1), cloxacinil (1), clozapine (3), cotrimoxazole (1), deferasirox (1), mefametic acid (1), piperacillin and tazobactam (1), sulfasalazine (1), ticlopidine (2)</td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>azathioprine (2), carbamazepine (1), deferasirox (1), fusidic acid (1), complementary medicine (1), methotrexate (1), phenytoin (1), teicoplanin (1), vancomycin (1)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>allopurinol (1), azathioprine (1), carbamazepine (2), cefuroxime (1), cefazoline (1), cotrimoxazole (1), deferasirox (1), mefenamic acid (1), piperacillin and tazobactam (1), sulfasalazine (1), ticlopidine (1), vancomycin (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>ciprofloxacin (2), frusemide (1), complementary medicines (2), metazapine (1), phenytoin (1), piperacillin and tazobactam (1), simvastatin (1), ticlopidine (2)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis, Hepatitis with jaundice</td>
<td>allopurinol (1), amoxicillin (1), atovastatin (1), azathioprine (2), cotrimoxazole (3), complementary medicines (10), chlorpromazine (1), dapone (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)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), SJS-TEN</td>
<td>allopurinol (5), amoxicillin (3), carbamazepine (15), cefalexin (1), ciprofloxacin (1), diethylaminoethanol (1), ethosuximide (1), esomeprazole (1), ethambutol (1), etoricoxib (1), flucloxacilinate (1), ganciclovir (1), ginkgo biloba (1), imipenem and cilastatin (1), isoniazid (1), levofloxacin (1), levetiracetam (1), mesalazine (1), minocycline (1), omeprazole (1), paracetamol (1), phenytoin (2), piperacillin and tazobactam (3), piroxicam (1), propranolol (1), pyridoxine (1), simvastatin (1), streptomycin (1), valproic acid (1), vancomycin (1)</td>
<td></td>
</tr>
</tbody>
</table>

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

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**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®, 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 (DHCL) in Europe to inform healthcare professionals of 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 acute 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 (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


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HA has approved the following package insert amendments reflecting safety issues.

1. Citracetamide (Citranex®, Novartis) Special warnings: Avoid exposure to light exposure due to risk of skin malignancy.

2. Concomitant use of other drugs which may cause intravenous catheters to become infected with minor catheter infections (e.g., outgrowth of bacterial biofilm on the catheter), leading to catheter tip dysfunction or infection. Avoid use within the availability of the package insert.

3. Captopril (Capoten®, Novartis) Special warnings: Several cases of severe hypotension have been reported. Caution should be exercised in patients receiving captopril who are also on diuretics, especially if the diuretic is an angiotensin-converting enzyme (ACE) inhibitor.

4. Diazepam (Valium®, Roche) Special precautions: Hypersensitivity, including anaphylaxis, is rare. Patients should be monitored for signs of anaphylaxis, including rash, urticaria, angioedema, bronchospasm, and laryngeal stridor. If anaphylaxis occurs, the drug should be discontinued and appropriate therapy should be administered.

5. Aprepitant (Emend®, MSD) Special precautions: Emend® affects the serotonin-1B/1D receptor. Caution is recommended in patients with history of serotonin syndrome.

6. Hydroxychloroquine (Plaquenil®, Sanofi-Aventis) Special warnings: Drug interaction with antacids containing calcium carbonate may reduce absorption of hydroxychloroquine.

The Health Sciences Authority (HSA) has requested Merck & Co Ltd to suspend the sales of 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 plaque 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 risk 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 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