HSA Health Sciences Authority

Adverse Drug Reaction news

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Serious skin reactions associated with allopurinol

HSA would like to alert healthcare professionals on a series of local suspected adverse drug reaction (ADR) reports of death associated with the use of allopurinol locally. Allopurinol, a widely prescribed xanthine oxidase inhibitor used in the treatment of hyperuricaemia, is known to cause serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that lead to significant morbidity and mortality.

Recent death reports associated with allopurinol

Four fatal cases linked to allopurinol use were reported to HSA over the first five months of 2009. Of these reports, three of the patients developed TEN while the fourth patient developed hypersensitivity syndrome to allopurinol. All of them were elderly patients (68-80 years old), with co-morbidities such as ischaemic heart disease, chronic renal failure, diabetes and hypertension. Three of the patients were on concurrent medications, such as vancomycin, frusemide and irbesartan which were also suspected to have contributed to the serious skin conditions.

In addition to the four death cases mentioned above, there were another 19 reports of fatality received over the period 1997 to 2008, of which 16 cases were associated with SJS, TEN or Allopurinol Hypersensitivity Syndrome (AHS).

Serious skin reactions associated with allopurinol

a) Local reports

The Pharmacovigilance Branch of HSA has received 183 local suspected ADR reports associated with allopurinol from 1993 to May 2009. Majority of these reports (80%) comprised skin reactions of which almost half of them included reactions such as SJS, TEN, AHS and erythema multiforme.

Allopurinol hypersensitivity syndrome (AHS) is a life threatening hypersensitivity reaction to allopurinol and is accompanied by symptoms such as fever, rash, leukocytosis, eosinophilia, hepatitis and acute renal failure.[1]

b) Overseas reports

From 2004 to 2008, a total of 2,541 global adverse drug reaction reports associated with allopurinol were reported in the WHO Vigibase*. Of these reports, more than 15% describe serious skin reactions namely, hypersensitivity reactions (67 reports), SJS (233 reports) and TEN (107 reports).

** WHO Vigibase is a global database of reported adverse reactions to medicinal products, maintained and developed by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. It receives spontaneous ADR reports provided by national pharmacovigilance centres in more than 80 countries, including Singapore.*

HLA-B*5801 associated allopurinol-induced severe cutaneous adverse reactions (SCAR)

HLA-B*5801 allele has been identified as a genetic marker for severe cutaneous adverse reactions (SCAR) caused by allopurinol. In a pharmacogenetic study on allopurinol-induced SCAR[2], a strong association of the allele HLA-B*5801 with the susceptibility of allopurinol-induced AHS, SJS and TEN in Han Chinese was identified. Although other ethnic patients with allopurinol-induced SCAR were not included in the study, it was suggested that this association may also exist in other ethnic groups as HLA-B*5801 is also present in other populations (7% in African, ~ 2-7% in Caucasian, and 8% in Asian Indian).

HSA's earlier advisory on the use of allopurinol

In 2001, the Pharmacovigilance Branch conducted a safety assessment of all local spontaneous ADRs associated with the use of allopurinol and found that 50% of the ADRs reported with allopurinol were serious skin reactions such as SJS, TEN and AHS. In addition, two local studies[3,4] revealed 18 cases of serious local reports of ADRs to allopurinol which comprised mainly of AHS. In view that these adverse reactions are associated with significant morbidity and mortality, a Dear Healthcare Professional Letter[5] was issued to advise doctors on the appropriate use of this drug.

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Voluntary recall of Hydroxycut® products in Singapore

Hydroxycut® products have been voluntarily recalled in Singapore by its supplier on 4th May 2009 due to overseas reports of liver toxicity suspected to be associated with the products. The products have been recalled in the United States on 1st May 2009.

Hydroxycut® products are marketed for weight-loss (fat burners, energy-enhancers, low carb diet aids, and for water loss) and are distributed by Global Active Limited in Singapore through GNC outlets and other retail outlets, including pharmacies. They are also sold over the Internet.

Cumulative reports received by the US FDA

The US Food and Drug Administration (FDA) has received 23 cumulative reports of serious adverse reactions affecting the liver including one death due to liver failure over the period of 2002 to 2009. These reports ranged from asymptomatic hyperbilirubinemia and jaundice to liver damage and liver transplants. The age range of patients in the reports was between 21 to 51 years of age and liver injury occurred even when the patients said they had taken doses according to those recommended on the bottle. No other causes for liver disease were identified. In the majority of the patients, no pre-existing medical conditions that predisposed the consumer to liver injury could be identified other than the consumption of the implicated products. Amongst the cases, there were some in which the patients' liver function recovered after discontinuation of Hydroxycut® usage.

Currently, the US FDA is unable to determine exactly which ingredient or combinations of ingredients in Hydroxycut® products may be responsible for the liver injury. It is also undeterminable if other factors such as the patient's health condition, length of use, dosage, or concomitant administration with other drugs or supplements may increase the risk of liver toxicity associated with Hydroxycut® products.

Although the incidence of liver damage appears to be relatively rare in relation to the usage of Hydroxycut® products, these products have been assessed to pose a serious public health risk. Other serious adverse reports received by the US FDA in association with Hydroxycut® products include rare reports of seizures, rhabdomyolysis, and cardiovascular disorders ranging from palpitations to heart attack.

Local situation and HSA advisory

To-date, no local reports of adverse reactions have been received in relation to the consumption of Hydroxycut® products.

In a press release issued on 3rd May 2009, HSA advised consumers who have been taking Hydroxycut® products to stop taking them immediately and to discard them. Consumers were also advised to seek medical attention should they experience any adverse reactions or feel unwell after taking their medicines.

Healthcare professionals are encouraged to inquire about their patient's consumption of health supplements and herbal products when taking their medical history, especially in the setting of a suspected drug-related liver toxicity. Healthcare professionals are encouraged to report adverse reactions suspected to be associated with the use of complementary medicines to the Pharmacovigilance Branch.

References

1. *FDA News Release. May 1, 2009. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149575.htm*
2. *FDA letter to Healthcare Professionals on the Potential Risk of Severe Liver Injury from the Use of Hydroxycut Dietary Supplements. http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm155847.htm*

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■ Serious skin reactions associated with allopurinol ■

In the advisory, doctors were advised to prescribe allopurinol with care for the treatment of:

1. Recurrent episodes of acute gout unresponsive to prophylactic colchicines and when uricosuric agents cannot be used due to intolerance, lack of efficacy, renal insufficiency or poor patient compliance
2. Chronic tophaceous gout
3. Recurrent uric acid calculi
4. Recurrent calcium oxalate renal calculi when associated with hyperuricosuria
5. Prevention of acute urate nephropathy in patients receiving cytotoxic therapy for malignancies

In particular, doctors were also advised that the dose of allopurinol should be reduced in patients with impaired renal function.

HSA's Advisory

Healthcare professionals should be mindful of the local cases of serious skin reactions associated with allopurinol and exercise caution with the use of this drug during treatment of hyperuricaemia and its complications, including its prophylactic use in the prevention of hyperuricaemia associated with cancer treatment.

As early signs of rash and skin reactions may be indicative of a more serious reaction such as SJS or AHS, healthcare professionals are advised to educate their patients on early recognition of allergic reactions, on the importance of prompt withdrawal of the drug at the first sign of rash and to seek medical advice.

Healthcare professionals are encouraged to continue reporting suspected ADRs associated with allopurinol to the Pharmacovigilance Branch of HSA.

References

1. *Singapore Med J 2008; 49 (5): 384 – 7.*
2. *Proc. Natl. Acad. Sci. USA; Apr 05, Vol 102, No 11, 4134-9. http://www.pnas.org/cgi/doi/10.1073/pnas.0409500102.*
3. *Singapore Med J 2000; 41: 156 – 60.*
4. *Thong B YH, Leong KP, Chng HH. Allopurinol hypersensitivity syndrome in a general hospital (abstract). 34th Singapore-Malaysia Congress of Medicine/Combined Hospitals Medical and Dental Scientific Meeting, 3-6 Aug 2000, Singapore.*
5. *HSA Drug Safety Information. Risk Assessment of Allopurinol. 22 Oct 2001.*

Electronic package inserts on HSA website

HSA is pleased to announce that the electronic versions of Package Inserts (PI)/Patient Information Leaflets (PIL) for all new medicinal products registered since 2003 are now available via the "Online Information Search (Infosearch)" function on the HSA website (http://www.hsa.gov.sg/infosearch).

All healthcare professionals can now access the current approved PI/PIL for more than 1000 medicinal products via the HSA website. Please contact Ms Sherly Tanjung at 6866 1040 or email HSA_PBB_Productlabels@hsa.gov.sg should you have any feedback on the above new e-service.

Reporting vaccine-related adverse events

The Pharmacovigilance Branch (PVB) of the Health Sciences Authority (HSA), besides administering the national spontaneous adverse drug reaction reporting programme for drugs, also manages the vaccine safety monitoring programme. The function of detecting and assessing safety signals from adverse event reports related to vaccines was transferred from the Ministry of Health to the PVB in 2007.

Challenges in vaccine safety monitoring

As in the case of drugs, no vaccine is 100% safe or effective. However, unlike drugs which are administered to patients mainly for treatment purposes, vaccines are generally given to healthy people, to prevent diseases. Hence, the tolerance (by the public, policy-makers and healthcare professionals) of vaccine-related adverse events is substantially lower than for therapeutic products. A very high standard of safety is also expected of vaccines as large numbers of people are inevitably exposed to vaccines on a regular basis once the vaccines are listed as part of the National Immunisation Programme.

To address the greater public health concerns of vaccine safety, it is critical to investigate the causes of all serious signals, especially the much rarer adverse events after vaccinations. For example, for vaccinees, events occurring at a frequency of one in a 100,000 to one in a million doses (eg. acute encephalopathy after whole-cell pertussis vaccine, Guillain-Barre syndrome after swine influenza vaccine in 1976) are of pertinence as compared to adverse reactions commonly associated with cancer chemotherapy or gastrointestinal adverse reactions experienced by 10-13% of patients on high-dose aspirin. Research designed to study such rare adverse events are costly and difficult to organise. Hence, the spontaneous reporting of adverse events to vaccines is a very useful tool to enable detection of such rare adverse events following immunization.

Reporting vaccine related adverse events locally

Locally, the national reporting of vaccine adverse events can be effected through the same spontaneous reporting channels as those used for reporting of adverse drug reactions. In the year 2008, forty vaccine-related adverse events were received by the PVB and a total of 562 adverse events to vaccines were reported from 1997 to 2008 (see figure 1).

a) Vaccine adverse event classification and causality assessment

Vaccine adverse events can be classified by frequency (common, rare), extent (local, systemic), seriousness (hospitalization, disability, death), causality, and preventability (intrinsic to vaccine, production-related, administration-related). The United States Centers for Disease Control and Prevention (CDC) classifies adverse events after vaccinations into: (1) vaccine-induced — due to the intrinsic characteristic of the vaccine preparation and the individual response of the vaccine; events which would not have occurred without vaccination (2) vaccine-potentiated — events which would have occurred anyway, but were precipitated by vaccination; (3) programmatic error — due to technical errors in vaccine preparation, handling or administration (4) coincidental — events associated temporally with vaccination by chance or due to underlying disease.

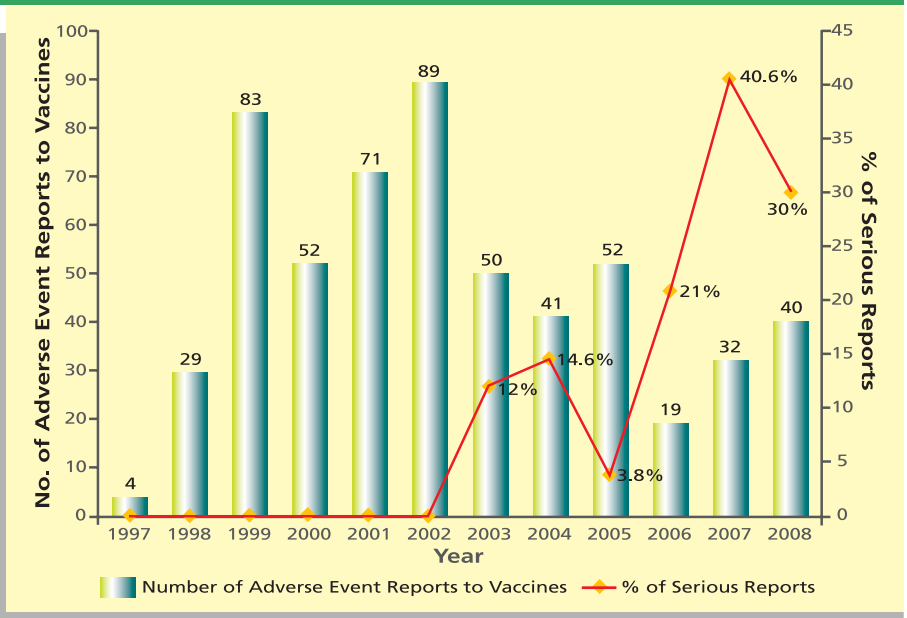

Fig.1 Local spontaneous reports of adverse reactions to vaccines received between 1997 and 2008

In the clinical setting, healthcare professionals can take a pragmatic approach to causality assessment by making the assumption that any adverse event which occur within a reasonable period of time (up to about 6 months) after vaccination may be caused by the vaccine, regardless of whether they are truly causal or coincidental. The PVB will then conduct a more in-depth assessment of the report, taking into account the following:

(1) the previous experience with the vaccine locally and internationally. This include the duration of the product on the market, degree of public exposure to vaccine, the consideration of whether similar events observed among other vaccinees or non-vaccinees (from international signals and literature), the existence of safety data from animal studies;
(2) alternative causes;
(3) individual characteristics of the vaccine that may increase the risk of the adverse event;
(4) timing of the event;
(5) characteristics of the event (e.g. laboratory findings); and
(6) rechallenge (if undertaken).

b) Additional details required for reporting of vaccine-related adverse events

As vaccines are biologically-derived products, additional information will be required on top of the usual fields as required on the Adverse Drug Reaction (ADR) reporting form for drugs. Pertinent information to aid in causality assessment of a vaccine-related adverse event include:

a) vaccine type,
b) manufacturer,
c) lot or batch number,
d) route of administration
e) the number of previous doses of vaccine given
f) the concurrent vaccinations which were administered at about the same time as the suspected vaccine.

It is recommended that as much details to be provided on the adverse events as possible. Minor reactions such as fever, local redness, swelling and pain may not necessarily be reported unless deemed to be medically significant.

Conclusion

All healthcare professionals are encouraged to report all serious adverse events suspected to be associated with vaccines to the PVB. A robust vaccine monitoring system in Singapore to safeguard public health cannot be achieved without the active participation of healthcare professionals.

References

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2. *Centers for Disease Control and Prevention (CDC). Vaccine Safety. http://www.cdc.gov/vaccinesafety/basic/history.htm*
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4. *World Health Organisation- Immunization Safety. http://www.who.int/immunization_safety/en/*

Update on drotrecogin alfa (Xigris®) and increased risk of bleeding

New data on patients with baseline bleeding risk factors

The HSA Pharmacovigilance Branch would like to bring to the attention of healthcare professionals a recent retrospective study that revealed an increase risk of death and serious bleeding events in patients with baseline bleeding tendencies treated with drotrecogin alfa (Xigris®, Eli Lilly)

Xigris® is a recombinant form of human activated Protein C, licensed in Singapore for the reduction of mortality in adult patients with severe sepsis (i.e. sepsis associated with acute organ dysfunction) who have a high risk of death. It has been registered in Singapore since August 2002.

Results from recent retrospective study

In February 2009, the US Food and Drug Administration (FDA) issued an early safety communication[1] about its ongoing safety review of Xigris®. The investigation stemmed from the results of a retrospective medical record review published in a recent issue of Critical Care Medicine.[2] This review was aimed at assessing the safety of Xigris® when used in patients with or without baseline bleeding risk factors. Findings from this review shed some light on the safety profile of drotrecogin alfa when used in patients with specific baseline bleeding risk factors, since this group of patients was excluded in earlier key clinical trials involving drotrecogin alfa. Seventy-three patients who received drotrecogin alfa from two tertiary care institutions between 2002 and 2005 were reviewed, regardless of whether they met indications according to product labeling or clinical practice guidelines.

The study revealed that serious bleeding events occurred in seven of 20 patients (35%) who were predisposed to bleeding tendencies (such as recent oral anticoagulant or platelet inhibitor therapy, severe hepatic disease, use of heparin, platelet count < 30,000/mm^3, recent gastrointestinal bleed and recent thrombolytic therapy) vs. only two of 53 (3.8%) patients without any bleeding tendencies. However, there were no clear trends by type of baseline bleeding risk factors and type or incidence of serious bleeding event. More patients with bleeding risk factors died (13 out of 20; 65%) compared with patients without any risk factors for bleeding (13 out of 53; 24.5%). In response to the above finding of an increased risk of death and serious bleeding events in patients with baseline bleeding risk factors treated with Xigris® , FDA is working with Eli Lilly to further evaluate the incidence of serious bleeding events and mortality in patients who receive Xigris®. In the meantime, the US FDA and Eli Lilly have recommended that prescribers carefully weigh the increased risk of bleeding against the benefits of Xigris® when using this drug.

Safety findings from earlier studies

Apart from the recent study described above, there had been other studies that investigated the risk of mortality associated with Xigris® in other specific patient groups. It is noteworthy that these trials excluded patients at high risk of bleeding.

Xigris® was approved by the FDA after the international, multi-centre, randomized, double blind, placebo trial of 1,690 patients with severe sepsis, Recombinant Human Activated PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS), demonstrated a significant reduction in mortality at 28 days, in patients receiving Xigris® compared to placebo (24.7% vs 30.8%, p=0.005).[3] Upon exploratory subgroup analysis, significant absolute death reduction was found to be limited to the subgroup of patients with greater disease severity, i.e. baseline APACHE II score >25 or at least 2 acute organ dysfunctions at baseline but not in the subgroup of patients with lower disease severity.[4]

Following the approval of Xigris®, ADDRESS[5] (Administration of Drotrecogin Alfa in Early Stage Severe Sepsis), which investigated the efficacy and safety of drotrecogin alfa (activated) in adult patients with early stage severe sepsis (i.e. a lower risk of death), was conducted. This study was terminated early based on a low likelihood of detecting statistically significant reduction in the 28-day mortality in patients at low risk of death from sepsis. A post hoc analysis of the ADDRESS clinical trial database and reanalysis of the PROWESS clinical trial database were carried out. The results of these analyses showed higher 28-day and in-hospital mortality (within 90 days after the start of infusion) and increased serious bleeding events in drotrecogin alfa patients with single organ dysfunction and recent surgery within 30 days prior to study treatment than those who received placebo.

In 2005, the RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE)[6] trial was stopped following a numerical increase in the rate of central nervous system (CNS) bleeding in the Xigris® versus the placebo group. Over the six-day infusion period, the number of patients experiencing CNS bleeding was five versus one (2.1% drotrecogin alfa versus 0.4% placebo). Fatal CNS bleeding events, serious bleeding events, serious adverse events and major amputations were similar in the drotrecogin alfa and placebo groups. Xigris® is not indicated for use in paediatric patients with severe sepsis.

Local Situation

To date, HSA has received one suspected local ADR report of diffuse cerebral haemorrhage in a 62 year old male, probably related to the use of Xigris® for severe sepsis. The adverse event occurred a day after Xigris® was administered at a therapeutic dose of 1.55mg/hr for 96 hours. It is not known if the patient had presdisposing risk factors for bleeding.

In light of the new data from the recent retrospective study, healthcare professionals are encouraged to carefully weigh the benefits versus risk of using Xigris® in patients predisposed to bleeding. Healthcare professionals are also encouraged to report suspected adverse drug reactions associated with drotrecogin alfa to the Pharmacovigilance Branch of HSA.

References

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2. *Crit Care Med 2009;37(1):19-25.*
3. *New Eng J Med, Vol. 344, No. 10:699-709.*
4. *http://www.fda.gov/CDER/drug/early_comm/drotrecogin_alfa.html*
   APACHE II score >25. The APACHE II score (Acute Physiology and Chronic Health Evaluation II) is a commonly-used severity of disease classification system calculated for critically ill patients after admission to an intensive care unit.
5. *New Eng J Med, Vol. 353, No.13: 1332-1341.*
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Traditional medicines adulterated with steroids

Adulterants detected in "Bao Ling Capsule", "Air Ikan Haruan Extract", "Delima Raja Ura" & "Cao Gen Bai Ling Wan"

In recent months, the Pharmacovigilance Branch of HSA has received four reports of adverse drug reactions from our healthcare professionals, leading to the detection of adulterated traditional medicines.

Report on "Bao Ling Capsule"

In the first report, a general practitioner observed that a 52-year-old female patient had developed facial swelling, a buffalo hump, increased frequency of urine and enhanced thirst after consuming a product labelled "Bao Ling Capsule" (保灵丸) to relieve her symptoms of rheumatoid arthritis. The patient had consumed the product for about six months and reported that she purchased the product from a friend. The reporting doctor was certain that the patient did not have these symptoms before and Cushing's syndrome was suspected. The doctor also ruled out other possible contributory factors such as the consumption of other concomitant medicines.

The product sample was immediately sent to HSA for analysis. The analyses revealed the presence of three adulterants, namely betamethasone, hydrochlorothiazide and chlorpheniramine. The patient was reported to have taken three capsules daily, which corresponded to the therapeutic dose of each ingredient — betamethasone 2.7mg (therapeutic range: 0.5-5 mg daily), hydrochlorothiazide 51.3 mg (therapeutic range: 25-100 mg daily), and chlorpheniramine 11.5 mg (therapeutic range: 4-24 mg daily).

Report on "Air Ikan Haruan Extract"

In the second report, a 67-year-old female patient presented at the hospital with generalized malaise, widespread body aches, loss of appetite and sudden weight loss of 10 kg over 4 months. These unexplained symptoms prompted the doctor to enquire about the patient's medication history, which revealed that she was self-medicating with a traditional medicine labelled "Air Ikan Haruan Extract" for pain relief. The product was bought from Malaysia and patient had been taking it for more than one year until it was stopped recently.

Suspecting the presence of steroids in the product, the doctor submitted the liquid sample to HSA which was subsequently tested by the laboratory to contain dexamethasone at 0.093mg/ml. Based on the daily consumption of two tablespoons, the dose of dexamethasone consumed by the patient on a daily basis was 2.8 mg, which falls within the therapeutic range of 0.5-20 mg daily.

Report on "Delima Raja Urat"

In the third report, a 50-year-old female patient showed elevated fasting blood glucose level on repeated tests and was diagnosed to have diabetes mellitus by her general practitioner. The doctor found out that the patient was taking a Jamu product labelled "Delima Raja Urat", for relief of rheumatism and body ache for the past one month.

Upon testing, the product sample was found to contain dexamethasone and traces of chlorpheniramine, pheniramine and sibutramine. The patient followed the dosing on the product's label and took one capsule twice daily. This worked out to 1.0 mg of dexamethasone, 1.0 mg of chlorpheniramine, 1.6 mcg of pheniramine and 2.4 ng of sibutramine consumed on a daily basis. Except for dexamethasone, the other components were present at sub-therapeutic doses.

The hyperglycaemic symptoms and development of diabetes could have been the adverse effects of prolonged intake of dexamethasone.

Report on "Cao Gen Bai Lin Wan"

In the fourth report, a 74 year-old patient developed Cushingoid features such as facial flushing, weight gain and thinning of skin after taking the product "Cao Gen Bai Lin Wan" (草根百齡丸) for relief of joint pain for more than two months.

The product was subsequently tested by HSA to contain dexamethasone and chlorpheniramine. The product's recommended dose of two pills taken twice a day worked out to 1.5 mg of dexamethasone and 4.7 mg of chlorpheniramine, which was a therapeutic dose unwittingly consumed by the patient on a daily basis.

HSA's advisory

Prolonged use of corticosteroids such as dexamethasone and betamethasone may cause myopathy, osteoporosis, adrenal suppression, Cushing's syndrome and obesity. Symptoms of abrupt steroid withdrawal may include myalgia, arthralgia and weight loss, which were the symptoms manifested by the patient in the second case report upon stopping the consumption of the adulterated product.

HSA would like to remind healthcare professionals to consider the possible contribution of adulterated complementary health products when a patient presents with unexplained adverse symptoms without a plausible medical cause. Many patients may not proactively volunteer information on the consumption of such products to their healthcare professionals as they may not regard such products as medicines. A careful taking of patient's medical history is encouraged as it may elicit important and useful information relevant to the diagnosis of the patient's condition.

Oral sodium phosphates (OSP) and renal toxicity

Higher doses of OSP associated with serious adverse effects

HSA would like to update healthcare professionals on recent overseas reports of serious adverse events of acute kidney injury associated with the use of oral sodium phosphates (OSP). OSP are indicated for relief of occasional constipation or for preparing the bowel for medical procedures. While there are no major safety concerns when used as laxatives, their use for bowel cleansing (at higher doses) have been associated with serious adverse effects such as acute phosphate nephropathy.

Locally, OSP are available over-the-counter as General Sales List (GSL) products. Examples of OSP that are available in Singapore are *Fleet Phospho-Soda® Buffered Saline Laxative, Fleet Phospho-Soda® Oral Saline Laxative Ginger-Lemon* and *Phosphates Solution®*.

Reports received by US FDA

On 11 December 2008, the US Food and Drug Administration (FDA) reported having received 20 cases of kidney injury associated with the use of OsmoPrep®, a product containing OSP available only on prescription in the United States. Three of these patients were biopsy-proven cases of acute phosphate nephropathy. Concomitant use of an ACE inhibitor or angiotensin receptor blocker was noted in 11 cases, diuretic use in six cases, NSAID use in four cases, and one patient received a contrast dye. The onset of kidney injury in these reports were varied, in some cases occurring within several hours of use of these products and in other cases up to 21 days after their use.

Reports received by Health Canada

Health Canada (HC) has also received 53 adverse reaction reports in association with OSP, of which 30 case reports involved kidney dysfunction including 27 reported as serious. Other adverse reactions included gastrointestinal symptoms, cardiovascular and neurological problems and allergic reactions.

Acute phosphate nephropathy

Acute phosphate nephropathy is the result of the formation of calcium-phosphate crystals depositing in the renal tubules. It is a rare and serious adverse event that has been associated with the use of OSP. This form of acute kidney injury may lead to permanent renal function impairment.

The risk factors associated with the development of acute phosphate nephropathy include

- Age (especially individuals over 55 years)
- A decreased intravascular volume (due to conditions such as congestive heart failure, cirrhosis, or nephrotic syndrome)
- Having baseline kidney disease (acute or chronic), bowel obstruction or active colitis
- Concomitant use of drugs that affect renal perfusion or function (such as diuretics, ACE inhibitors, angiotensin receptor blockers, and possibly NSAIDs).

Regulatory Actions

a) US FDA

As a precaution, the FDA is recommending that OSP prescription products be used with caution for bowel cleansing by individuals with the risk factors mentioned above. Additionally, FDA has strengthened the labeling of two prescription products, Visicol® and Osmoprep®. The manufacturers of these products are also required to include a medication guide and conduct post marketing studies to assess the risk of kidney injuries with their respective products.

The current available data on over-the-counter OSP (e.g. Fleet Phospho-Soda®) do not show a risk of acute kidney injury when they are used at doses for laxative purposes, which are lower than doses for bowel cleansing. However, the use of over-the-counter OSP for the purpose of bowel cleansing (at higher doses) will have the same risks as prescription OSP. FDA plans to amend the labelling conditions for over-the-counter OSP to address this concern. FDA is recommending that over-the-counter OSP not be used for bowel cleansing. Consumers were advised to only use OSP for bowel cleansing pursuant to a prescription from a healthcare professional.

b) Health Canada (HC)

An advisory was issued by HC on 5 Mar 2009 stating that although these products have a long history of safe use as laxatives, they have been associated with serious adverse effects, including electrolyte disturbances and kidney injury, when used as bowel cleansers. The instructions for purgative use on the labels of these products should no longer be followed, unless recommended by a health care practitioner. HC is working with companies marketing OSP products to update the labeling of the affected products.

Local Situation

The locally registered OSP already carry warnings against use in kidney disease and caution against use except under medical supervision/advice. Nevertheless, IDS Pharmaceutical Division had taken a precautionary measure to voluntarily recall their OSP product, i.e. Phosphates Solution® on 4 March 2009 although all stocks of Phosphates Solution® are not labeled for bowel cleansing.

In a further step to minimize risk to consumers and ensure the appropriate use of OSP products, HSA published a consumer advisory on HSA website recently to advise consumers to seek medical advice before using these products for bowel cleansing.

To date, HSA has not received any local reports of acute phosphate nephropathy associated with OSP. Nevertheless, healthcare professionals are advised to take into consideration this recent safety finding on OSP when prescribing them to patients. It is recommended that OSP be used with caution in patients who are at risk of developing acute phosphate nephropathy.

References

1. *FDA Alert [12/11/2008] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm*
2. *Health Canada Public Warning [5 March 2009]. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2009/2009_37-eng.php*

Package insert amendments reflecting safety issues

HSA has approved the following package insert changes due to safety updates from January 2009 to April 2009. 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. Alfentanil (Rapifen®, J&J) Special warning: Bradycardia & possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic agents, or when Rapifen® is combined with non-vagolytic muscle relaxants. Interactions: Metabolism of alfentanil may be inhibited by voriconazole. May need to lower dose of Rapifen® during concomitant use with propofol. New ADRs: Hyperhidrosis, hypercapnia, epistaxis, allergic dermatitis, postoperative confusion, neurological anaesthetic complication, endotracheal intubation complication, anaphylactic reaction, anaphylactoid reaction, loss of consciousness, convulsion, myoclonus, miosis, cardiac arrest, respiratory arrest.

2. Atenolol (Tenormin®, AstraZeneca) Interaction: Possible potentiating effect on atrial-conduction time & induce negative inotropic effect with amiodarone. ADR: Intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon.

3. Bupropion (Zyban®, GSK) Interactions: Caution when co-administering with drugs which affect CYP2B6 isoenzyme e.g. ticlopidine, clopidogrel. Increased doses of bupropion may be needed when receiving ritonavir. Maximum recommended dose of bupropion should not be exceeded. New ADRs: Delusion, paranoid ideation, restlessness, aggression.

4. Cetirizine & pseudoephedrine (Zyrtec-D®, UCB) Contraindications: 1) Severe renal insufficiency, uncontrolled hyperthyroidism, severe arrhythmias, 2) treatment with monoamine oxidase inhibitor (MAOI) & 2 weeks after MAOI discontinuation, 3) history of stroke, 4) in patients at high risk of developing haemorrhagic stroke. Special warnings: Increased risk of haemorrhagic stroke with concomitant use of vasoconstrictors e.g. bromocriptine, pergolide, due to risk of vasoconstriction & increased BP. Caution in patients at risk for hypercoagulability (e.g. inflammatory bowel disease) and in hypertensive patients treated with NSAIDs, as both pseudoephedrine & NSAIDs can increase BP. Interactions: Proton pump inhibitors, halogenated anaesthetic agents. New ADR: Stroke. Pregnancy: May increase frequency of gastroschisis & may induce a reduction in uteroplacental circulation.

5. Cyproterone (Androcur®, Bayer Schering) Warnings: Patients with previous arterial or venous thrombotic/ thromboembolic events, a history of cerebrovascular accidents or advanced malignancies are at increased risk of further thromboembolic events. Interactions: Inducers of CYP3A4 e.g. rifampicin, phenytoin & St. John's wort may reduce levels of cyproterone acetate. HMGCoA inhibitors & high doses of cyproterone may interact and increase risk of rhabdomyolysis. New ADRs: Decreased libido, increased libido (women), erectile dysfunction, hot flushes & sweating (men), jaundice, increased liver enzymes, thrombotic phenomena, mastodynia, irregular menstrual cycles, dysmenorrhoea, vaginal discharge, skin discolouration, striae, hepatitis, hepatic failure, tachycardia, galactorrhoea, sleep disturbances, severe disturbances of liver function, benign cerebral meningiomas.

6. Diclofenac (Cataflam®, Voltaren®, Novartis) New ADRs: Hepatic necrosis, hepatic failure.

7. Doxazosin (Cardura®, Pfizer) Special warning: Intraoperative Floppy Iris Syndrome (IFIS) observed during cataract surgery in patients on or previously treated with α1-blockers. Caution in current or past users of α-blockers due to increased risk of procedural complications during surgery when IFIS present. New ADR: IFIS.

8. Erlotinib (Tarceva®, Roche) Interactions: potent CYP3A4 inhibitors e.g. azole antifungals, protease inhibitors, erythromycin or clarithromycin, combined CYP3A4/CYP1A2 inhibitors, cigarette smoking, drugs reducing gastric acid production. New ADRs: Hirsutism, paronychia, eyelash/eyebrow changes, brittle & loose nails. Special populations: Administer cautiously to patients with hepatic impairment. Reduce dose or discontinue Tarceva® if severe ADRs occur.

9. Fentanyl (Fentanyl®, J&J) Interactions: Co-administration of fluconazole or voriconazole & Fentanyl® may result in increased exposure to Fentanyl®. Plasma clearance of midazolam affected by simultaneous administration of Fentanyl® with IV midazolam. New ADRs: Sedation, dyskinesia, visual disturbance, tachycardia, arrhythmia, hypertension, vein pain, allergic dermatitis, postoperative confusion/ agitation, neurological anaesthetic complication, euphoric mood, blood pressure fluctuation, phlebitis, hiccups, hyperventilation, hypothermia, anaphylactic shock, convulsions, loss of consciousness, cardiac arrest.

10. Gentamicin, zirconium (Septopal®, Merck) Special warning: Local hypersensitivity reactions reported. Pregnancy & lactation: Should not be used in 1st trimester; Should only be used in vital indications during further stages of pregnancy. Lactation: Infant should be weaned.

11. Ipratropium, fenoterol (Berodual®, Berodual® & Duovent®, Boehringer Ingelheim) Special precautions: Immediate hypersensitivity reactions may occur after administration. Post-marketing data & published literature of rare occurrences of myocardial ischaemia associated with B-agonists. Interactions: MAOIs, TCAs & sympathomimetic agents. New ADRs: Increased heart rate, glaucoma, laryngospasm, anaphylactic reactions, atrial fibrillation, supraventricular tachycardia, pharyngitis, myocardial ischaemia.

12. Letrozole (Femara(®, Novartis) New ADRs: Hepatitis, toxic epidermal necrolysis, erythema multiforme.

13. Losartan (Cozaar®, MSD) Interactions: lithium salts, NSAIDs, selective COX-2 inhibitors, angiotensin II receptor antagonists. New ADRs: Thrombocytopenia, arthralgia, dysgeusia, erectile dysfunction/impotence, erythroderma, photosensitivity, vomiting, malaise.

14. Mefenamic acid (Fenagesic®, Sunward Pharma) NSAIDs can cause serious cutaneous adverse events (rare) e.g. exfoliative dermatitis, toxic epidermal necrolysis (TEN) & Stevens-Johnson Syndrome (SJS). Events are idiosyncratic & are independent of dose or duration of use. Safety & effectiveness in children below 14 years not established. Interaction: Lithium.

15. Mivacurium (Mivacron®, GSK) Warnings & precautions: Prolonged & intensified neuromuscular blockade following Mivacron® may occur secondary to reduced plasma cholinesterase activity in: 1) Physiological variation eg. during pregnancy & puerperium, 2) genetically determined abnormalities of plasma cholinesterase, 3) severe generalised tetanus, tuberculosis & other severe or chronic infections, 4) chronic debilitating disease, malignancy, chronic anaemia & malnutrition, 5) myxoedema & collagen diseases, 6) decompensated heart disease, 7) peptic ulcer, 8) burns, 9) end-stage hepatic failure, 10) acute, chronic or end-stage renal failure, 11) iatrogenic: following plasma exchange, plasmapheresis, cardiopulmonary bypass, & as a result of concomitant drug therapy. High rate of cross-sensitivity (>50%) between neuromuscular blocking agents reported.

16. Mometasone (Nasonex®, Schering-Plough) Precautions: During use in acute rhinosinusitis, if signs & symptoms of severe bacterial infection are observed advise patient to consult physician immediately. Treatment should not be initiated if symptoms are present at time of diagnosis. Safety & efficacy for treatment of acute rhinosinusitis in children <12 years not studied. New ADRs: Diarrhoea, nausea, abdominal pain.

17. Moxifloxacin (Avelox(®, Bayer) Contraindication: Patients < 18 years old.

18. Olanzapine (Zyprexa®, Eli Lilly) New ADR: Changes in HDL cholesterol.

19. Oseltamivir (Tamiflu®, Roche) Undesirable effects: Post-marketing reports of convulsions & delirium (altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), very rarely resulting in accidental injury or fatal outcomes, primarily among pediatric & adolescent patients & often had an abrupt onset & rapid resolution. Such neuropsychiatric events are also reported in patients with influenza not taking Tamiflu®. New ADRs: Cardiac arrhythmia, visual disturbance.

20. Paliperidone (Invega®, J&J) Special warning/ Undesirable effect: Priapism.

21. Remifentanil (Ultiva®, GSK) Warning & precaution: Tachycardia, tachypnoea, hypertension & agitation reported infrequently upon abrupt cessation, esp. after prolonged administration.

22. Sibutramine (Ectiva®, Reductil® & Reduxade®, Abbott) New ADRs: Psychosis, mania.

23. Sorafenib (Nexavar®, Bayer) New ADRs: Cholecystitis, cholangitis, renal failure. Monitoring of fluid balance & electrolytes in patients at risk of renal dysfunction is advised.

24. Sunitinib (Sutent®, Pfizer) Special warnings: Baseline laboratory measurement of thyroid function recommended & hypothyroidism or hyperthyroidism to be rectified before treatment. Rare cases of hyperthyroidism, followed by hypothyroidism reported. Undesirable effects: Thrombotic microangiopathy (rare), proteinuria, nephrotic syndrome (rare). Baseline urinalysis recommended & monitor patients for proteinuria. Discontinue in patients with nephrotic syndrome.

25. Tamoxifen (Nolvadex®, AstraZeneca) Contraindication: pregnancy. Special warnings: Increased incidence of endometrial changes including hyperplasia, polyps, cancer & uterine sarcoma (mostly malignant mixed Mullerian tumours) reported. Promptly investigate any patient receiving or having previously received Nolvadex®, or who presents with menstrual irregularities, vaginal discharge & symptoms e.g. pelvic pain or pressure. 2–3x increase in risk for venous thromboembolism (VTE) demonstrated in healthy tamoxifen-treated women. Screen patients at prothrombotic risk for thrombophilic factors. Risk of VTE further increased by severe obesity, increasing age, concomitant chemotherapy & all other risk factors for VTE. Long-term anticoagulant prophylaxis may be justified for patients who have multiple risk factors for VTE. Interactions: When used with cytotoxic agents, consider thrombosis prophylaxis. Undesirable effects: Reduce dosage to not < 20mg/day for severe side effects. Stop treatment if side effects persistent. Optic neuropathy & optic neuritis reported & in some cases resulting in blindness. Increased incidence of ischaemic cerebrovascular events reported. Leg cramps reported commonly in patients. Not recommended in children as safety & efficacy not established.

26. Thyroxine (Eltroxin®, GSK) Warnings: Careful dosage titration & monitoring necessary during initial titration period. Treatment in patients with panhypopituitarism or causes predisposing to adrenal insufficiency may cause dizziness, weakness, malaise, weight loss, hypotension & adrenal crisis. Interactions: Antacids, bile acid sequestrants, cation exchange resins, sucralfate, calcium carbonate, ferrous sulphate, oral contraceptives, oestrogen, tamoxifene, clofibrate, methadone, 5-fluorouracil, HMG-CoA reductase inhibitors (statins), androgens & anabolic steroids, imatinib, amiodarone. New ADRs: Seizure, pseudotumour cerebri (benign intracranial hypertension esp. in children), heart failure, myocardial infarction, dyspnoea, hair loss, decreased bone mineral density, menstrual irregularity, impaired fertility.

Excessive dose may result in craniosynostosis in infants, & premature closure of epiphyses in children resulting in compromised adult height.

27. Zafirlukast (Accolate®, AstraZeneca) Special warnings: Elevations in serum transaminases during treatment usually asymptomatic & transient but could represent early evidence of hepatotoxicity & very rarely been associated with more severe hepatocellular injury, fulminant hepatitis & liver failure, some resulted in fatal outcome. Very rare cases of fulminant hepatitis & liver failure reported in patients in whom no previous clinical signs or symptoms of liver dysfunction were reported.

Reports of warfarin-glucosamine interaction

Glucosamine reported to potentiate the effect of warfarin activity

In view of the popular use of complementary medicines locally, HSA would like to highlight to healthcare professionals the potential drug interaction between warfarin and glucosamine. Glucosamine is a health supplement available in a large variety of products and used for the symptomatic relief of osteoarthritis.

Reports from Australia TGA[1] and UK MHRA[2]

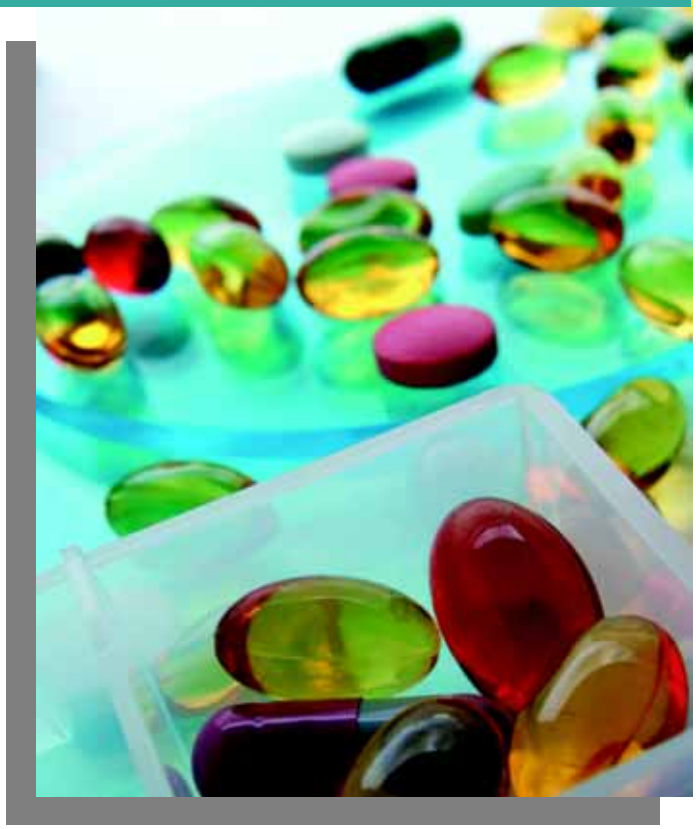
The Australian Therapeutic Drugs Administration (TGA) has received 12 reports describing a possible interaction between warfarin and glucosamine. From the reports, it was found that patients previously stabilised on warfarin experienced changes in the International Normalised Ratio (INR) after they started taking glucosamine. In ten out of the 12 cases, the patients had an increase in the INR whilst a slight fall in INR was observed in the other two cases. The peak INR ranged from 4.1 to 12 in eight of the cases. It was observed that the INR change ranged from 4 to 20 days after commencing glucosamine and in one case, the INR rise occurred two days after the dose of glucosamine was increased. Most of the INR increases did not lead to any complications except for hyphaema in one patient and haemoptysis and petechiae in another patient.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has also received seven reports suggesting an interaction between glucosamine and warfarin. In those cases, patients on warfarin therapy who previously had a stable INR experienced an INR increase after they started taking glucosamine.

Reports from the WHO-ADR database[3]

In a separate report from the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring, 22 spontaneous cases of suspected warfarin-glucosamine interaction originating from Australia, Canada, Denmark, Sweden, United Kingdom and the United States were filtered from the WHO-Adverse Drug Reaction database. An increased effect of warfarin was documented in 21 patients and one case involved decreased effect of warfarin. Two of the 22 patients were concomitantly using chondroitin, another health supplement also for the relief of arthritic pain.

Among the 21 cases of elevated INR, the event resolved when glucosamine was discontinued in 17 cases. Eleven of the patients had been chronic users of warfarin before the increased effect was established. The onset of increased INR was detected within three weeks in eight patients and within one to six months in five patients. In nine cases, the event required medical attention, hospitalization or closer INR monitoring. Four cases required prolonged hospitalization and/or the antidote vitamin K to reverse the effects of warfarin. One patient had an increase in INR three days after switching from glucosamine hydrochloride 750mg to glucosamine sulfate 1g, which suggested a dose effect.



The mechanism of interaction between warfarin and glucosamine remains unclear. It has been postulated that there is a possible pharmacodynamic interaction between glucosamine (a chemical component of heparin) and warfarin.[3] Animal studies have shown that glucosamine has an inhibitory action on platelets in vivo, by suppressing platelet aggregation, ATP release and thromboxane A_2 production.[4]

Conclusions

The Pharmacovigilance Branch has not received any local reports of INR changes associated with warfarin-glucosamine interaction.

Healthcare professionals are advised to monitor INR closely and titrate warfarin doses accordingly in patients on warfarin treatment who are consuming or commencing glucosamine or other complementary and herbal medicines. The INR of patients should also be monitored when there is a change in the dosing of complementary medicines.

References

1. *Australian Adverse Drug Reaction Bulletin, Vol. 27, No.1, Feb 2008.*
2. *MHRA/CSM. Current Problems in Pharmacovigilance 2006; 31:8.*
3. *Drug Safety 2006: 29:911.*
4. *Inflamm Res. 2005 Dec; 54(12):493-9.*

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