ACE inhibitors exposure in 1st trimester & congenital malformations

"New study suggests that congenital malformations may be associated with ACE inhibitors exposure in early pregnancy."

HSA would like to bring the attention of healthcare professionals to a recent study published in the New England Journal of Medicine [NEJM] which suggests that there is an increased risk of major congenital malformations in infants exposed to angiotensin-converting enzymes (ACE) inhibitors during the first trimester of pregnancy when compared with infants who had no exposure during first trimester.

The new finding is in contrast to the knowledge that ACE inhibitors, whilst contraindicated during the second and third trimester due to the known risk of fetopathy, has generally not been linked to adverse birth outcomes when used in the first trimester.

Details of study
The study concerned is an observational cohort study which included 29,507 infants born between 1985 and 2000 whose mothers had no evidence of diabetes before or during pregnancy. The authors identified 209 infants with exposure to ACE inhibitors in the first trimester alone, 202 infants with exposure to other antihypertensive drugs in the first trimester alone, and 29,096 infants with no exposure to antihypertensive drugs at any time during gestation. They found that infants exposed to ACE inhibitors were at an increased risk for major congenital malformations (risk ratio 2.71; 95% confidence interval, 1.72–4.27), as compared to those with no exposure to antihypertensive medications. The former group had an increased risk for malformations of cardiovascular system (risk ratio 3.72; 95% confidence interval, 1.89–7.30) and the central nervous system (risk ratio 4.39; 95% confidence interval, 1.37–14.02). In contrast, foetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio 0.66; 95% confidence interval, 0.25–1.75).

Conclusion
The ACE inhibitors that are available locally include captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril and ramipril.

The use of ACE inhibitor is contraindicated during the second and third trimesters of pregnancy. In utero exposure during this period is associated with ACE inhibitor fetopathy, a group of conditions that includes oligohydramnios, intrauterine growth retardation, renal dysplasia, anuria, renal failure and death. Although the above findings of an increased risk in first trimester use is considered preliminary due to the nature of the study and the small number of birth defects in the study group, healthcare professionals should take these findings together with other information about a patient’s medical situation during early pregnancy. The current labelling generally recommends discontinuation of the ACE inhibitor as soon as possible if a patient becomes pregnant.

HSA will continue to monitor this emerging safety concern and take appropriate regulatory actions such as strengthening of the package inserts of the affected drugs to reflect this safety concern when necessary.

Hepatitis B reactivation associated with Enbrel®, Humira® and Remicade®

Three anti-tumour necrosis factor alpha (anti-TNFα) agents are registered in Singapore - etanercept (Enbrel®, Wyeth), adalimumab (Humira®, Abbott) and infliximab (Remicade®, Centocor). These products are indicated for the treatment of rheumatoid arthritis with Remicade® having additional indications for Crohn’s disease and ankylosing spondylitis.

Anti-TNFα agents exert their actions by binding to human TNF, which are pro-inflammatory and immunoregulatory cytokines. When TNF are overexpressed, they mediate chronic inflammation.

Post-marketing reports

Rare cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving anti-TNFα therapy. From 2003 to date, there are at least seven published cases of HBV reactivation associated with the use of these products.1-6 These seven patients were positive for HBV surface antigen prior to anti-TNFα treatment and the clinically active HBV infection occurred following a latency period ranging from 1–18 months after initiation of anti-TNFα therapy (mainly with infliximab). With the exception of one fatal case, the HBV conditions were controlled with discontinuation of anti-TNFα treatment followed by administration of lamivudine.

Regulatory actions

In Jan 2006, Health Canada issued a public advisory7 on the safety profile of these three products which include the following information:

- HBV reactivation has been reported very rarely in patients with chronic hepatitis B infection receiving the anti-TNFα agents: Enbrel®, Humira® and Remicade®.
- Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating anti-TNFα therapy. Those identified as chronic HBV carriers (i.e. surface antigen positive) should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several months following discontinuation of therapy.
- Reactivation of HBV is not unique to anti-TNFα agents and has been reported with other immunosuppressive drugs.

Local situation

HSA has not received any local report pertaining to HBV reactivation associated with the use of these products. However, we are working with the pharmaceutical companies to strengthen the local package inserts to include this new safety concern.

References

Termination of Long-Term Intervention on Fractures with Tibolone (LIFT) Study

Tibolone (Livial® 2.5mg, Organon) is a synthetic steroid with estrogenic, progestogenic and androgenic properties. It was licensed in Singapore since 1991 for the treatment of complaints resulting from natural or artificial menopause.

In Feb 2006, the product owner, Organon, announced that the Long-Term Intervention on Fractures with Tibolone (LIFT) study was halted after reaching its primary efficacy endpoint, of decreasing the risk of new vertebral fractures in elderly osteoporotic women. However, an increased risk of stroke (ischaemic and haemorrhagic) was found in the treatment group when compared to the control group.

The LIFT trial, a placebo-controlled randomized trial started in 2001, was designed to investigate the effect of tibolone in the prevention of fractures among 4,538 subjects with osteoporosis, whose average age at baseline was 68 (SD 5.2) years old. Participants were assigned to take either 1.25mg tibolone daily or placebo. The number of new vertebral fractures is 44 (2.1%) with tibolone and 85 (4.1%) with placebo, hazard ratio 0.5 (p=0.0003). However, a higher number of strokes was observed in the treatment group when compared to the control group in the first (2.4 years) years of treatment. Twenty-five (1.11%) cases of stroke was found with tibolone and 11 (0.49%) with placebo, hazard ratio 2.3 (p=0.02) •
Omniscan® (a gadolinium-containing contrast agent, GE Healthcare) is a nonionic contrast medium licensed by HSA in 1996 for body, cranial and spinal magnetic resonance imaging (MRI). It provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the central nervous system. Gadolinium-containing agents were first approved for clinical MRI use in 1988.

Post-marketing reports of NFD/NSF
Over a 4-year period up to Apr 2006, GE Healthcare has received 25 case reports of serious and unexpected reactions of nephrogenic fibrosing dermopathy (NFD) and nephrogenic systemic fibrosis (NSF) in association with the use of Omniscan®. Twenty of these were reported in Denmark and five in Austria.¹

Patients with NSF/NFD experience swelling and tightening of the skin, usually limited to the extremities. These conditions may develop over a period of days to several weeks. For most cases, the skin thickenings (as a result of fibrosis) inhibit the flexion and extension of joints, resulting in contractures.² In rare incidences, a rapid and fulminant disease course may occur and result in death by restricting effective ventilation, or by restricting mobility to the point of causing falls.

All patients who developed NSF/NFD had severely impaired renal function, with the majority receiving dialysis before Omniscan® was administered. The dose of Omniscan® given to the patients was within the standard dose range used for MR angiography. The onset of NSF/NFD from the time of administration of Omniscan® ranged from six days to three months. The demographics of the patients involved are listed in Table 1 below.

| Mean age of patients (years old) | 52.5 ± 10.8 |
| Number of male patients | 11 |
| Number of female patients | 14 |
| Number of patients on dialysis* | 20 |

*Includes both peritoneal dialysis and haemodialysis

Conclusion
To date, HSA has not received any report associated with NFD/NSF following the use of Omniscan® in Singapore. As a direct causal link between Omniscan® and NSF/NFD has not been established, GE Healthcare will be investigating further to obtain additional information regarding the connection of the disorder and the use of contrast media, including Omniscan®.

Healthcare professionals are reminded that the package insert of Omniscan® carries a special warning for its use in patients with severely impaired renal function (GFR <10ml/min) and that care should be exercised before using Omniscan® in such patients.

Other gadolinium-containing contrast agents registered in Singapore includes OptiMARK®, Magnevist® and MultiHance®. Healthcare professionals are encouraged to report any serious adverse reaction arising from these products to the Pharmacovigilance Unit of the HSA.

References
Package insert amendments reflecting safety issues

1. Calcitriol (Calcijex®, Abbott) Under “Precautions”, it is stated that use of vitamin D analogs & cardiac glycosides may result in cardiac arrhythmias. Its effects may be reduced in patients taking barbiturates or anticonvulsants. Corticosteroids may counter the effects of vitamin D analogs. Rare cases of hypersensitivity reactions including anaphylaxis & localised redness or pain at injection site have been reported.

2. Clarithromycin (Klacid®, Abbott) Contraindicated with concomitant use of ergotamine or dihydroergotamine.

3. Ciclosporin (Gengraf®, Abbott) New drug interactions documented with colchicine, quinopristin/dalfopristin, amiodarone, aristat & St John’s Wort. Ciclosporin potentially enhances the toxic effects of colchicine especially in patients with renal dysfunction. Close monitoring is required in patients concurrently taking digoxin or colchicine. Myotoxicity has been reported with concomitant administration with HMG-CoA reductase inhibitors.

4. Daunorubicin (Daunorubicin®, Pfizer) Contraindicated in pregnancy. New safety information added to the sections on cardiac toxicity & bone marrow depression. Significant hepatic or renal impairment can enhance the toxicity of recommended doses of daunorubicin. A rise in blood urea or uric acid can also occur with rapid destruction of leukaemia cells. Monitoring is thus required. Drug interaction includes vaccines & destruction of leukaemia cells. Monitoring is thus required in patients taking barbiturates or anticonvulsants. Corticosteroids may counter the effects of vitamin D analogs. Rare cases of hypersensitivity reactions including anaphylaxis & localised redness or pain at injection site have been reported.

5. Fluticasone (Flixotide®, GSK) Very rare cases of increased blood glucose levels reported. Ritonavir (a CYP3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations resulting in markedly reduced cortisol concentrations, Cushing’s syndrome & adrenal suppression. Caution should be exercised when CYP3A4 inhibitors e.g. ketoconazole are coadministered with fluticasone.

6. Lidocaine, Prilocaine (Emla Cream®, AstraZeneca) Patients with G6PD deficiency or congenital or idiopathic methaemoglobinemia are more susceptible to drug induced methaemoglobinemia; and if eye contact occurs, loss of protective reflexes may allow corneal irritation & potential abrasion.

7. Nimesulide (Nidal®, IDS Pharmaceuticals) Maximum dose is reduced to 100mg twice daily. Some new contraindications include patients with a history of hepatotoxic reactions to nimesulide, cerebrovascular bleeding, severe coagulation disorders, severe heart failure, children under 12 years, third trimester of pregnancy & lactation. Avoid concomitant administration of anti-platelet drugs & alcohol abuse. New drug interactions include valproic acid, lithium, methotrexate & ciclosporin.

8. Propafenone (Rytmonorm®, Abbott) Drugs that inhibit CYP2D6, CYP1A2 & CYP3A4 e.g. ketoconazole might lead to increased levels of propafenone. Propafenone should be used with caution in nursing mothers. New ADRs include hepatitis, anorexia, syncope, hepatocellular injury, jaundice & lupus syndrome.

9. Ritonavir (Norvir®, Abbott) Pancreatitis has been observed in patients receiving ritonavir, including those who developed hypertriglyceridaemia especially patients with advanced HIV.


11. Vinorelbine (Navelbine®, Orient Europharma) Contraindicated in patients with neutrophil counts <1,500/mm³ or with current or recent severe infection. New precautions: 1) dose limiting neutropenia where treatment should be delayed till recovery if neutrophil count <1500/mm³ & platelet count <75000/mm³. 2) In severe liver impairment, dose should be reduced by 33% & haematological parameters closely monitored. 3) Combination of Navelbine® with other bone marrow toxic drugs (e.g. cisplatin) may exacerbate myelosuppressive adverse effects. A new list of ADRs has been added. Navelbine® should not be used in pregnant or lactating patients.

12. Fluoxetine (Prozac Dispersible®, Eli Lilly) A new contraindication states that if fluoxetine has been prescribed chronically and/or at a high dose, a longer interval of discontinuation (>5 weeks) should be considered when switching to MAOI. Serious & fatal cases of serotonin syndrome have been reported in patients treated with fluoxetine & MAOI in close temporal proximity. It is warned that there is a possibility of suicide in depression which may persist till significant remission occurs. Cases of suicidal ideation & behaviours have been reported during fluoxetine/ antidepressant therapy or early after treatment discontinuation. Close supervision of high-risk patients is recommended.

Other products with labelling changes include Cefuroxime [Zinna®, GSX], Fluvoxamine [Fluvoxamine®, Steward Cross], Glimperide [Amary®, Aventis], Nifuroxazide [Erecury®, Sanofi-Synthelabo], Olanzapine [Zyprexa®, Eli Lilly], Paroxetine [Anzotax®, Mayne Pharma], Phenobarbital injection [Mayne Pharma], Prazosin [Minipress®, Pfizer], Salometrol [Serevent®, GSX], Vancomycin [Vancomycin®, Hospira Inc].
Potential risk of cutaneous vasculitis toxicities associated with hydroxyurea

Bristol-Myers Squibb (BMS) has issued a Dear Healthcare Professional Letter (DHCPL) in the USA to notify healthcare professionals of new safety information on hydroxyurea (Hydrea®).

Hydrea® was approved for use in Singapore in 1995. It is indicated for melanoma, resistant chronic myelocytic leukaemia, and recurrent, metastatic, or inoperable carcinoma of the ovary. It is also indicated for concomitant therapy with irradiation therapy in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

New warnings
In its DHCPL, BMS warned that cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have been reported with the use of hydroxyurea in patients with myeloproliferative disorders. These vasculitic toxicities were reported most often in patients with a history of, or concurrently receiving interferon therapy. Due to potentially serious clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, BMS advised that hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop.

Reminder on safe handling of hydroxyurea
Further to this safety alert, there was also a reminder by BMS for patients to handle hydroxyurea with care. To decrease the risk of exposure to hydroxyurea by people who are not taking the medicine (such as caregivers), impervious disposable gloves should be worn when handling hydroxyurea or the bottles containing hydroxyurea. Anyone handling hydroxyurea should wash their hands before and after contact with the bottle or capsules and spillage of powder from the capsule should be wiped up immediately with a damp disposable towel and discarded in a closed container (e.g. plastic bag).

The local package insert of Hydrea® will be updated to reflect the latest safety warnings and instructions for safe handling of hydroxyurea. For more information, please refer to the DHCPL posted on the FDA website on http://www.fda.gov./medwatch/safety/2006/safety06.htm#Hydrea

Case report of adverse reactions with Baike Wan®, Shen Loon She (SLS)

A 66 year-old male patient was reported to develop acute on chronic renal failure with cardiopulmonary collapse secondary to hyperkalaemia after the consumption of a traditional medicine, Baike Wan®, obtained from Malaysia. The product was labelled to contain herbal ingredients and indicated for the relief of muscle and joint pain.

Analytical tests revealed the presence of three potent pharmaceutical drugs namely chlorpheniramine, frusemide and piroxicam. Based on the recommended daily intake on the label, the patient would be consuming about 7mg of chlorpheniramine, 11mg of frusemide and 30mg of piroxicam daily (within therapeutic doses). According to the Malaysian Regulatory Authority, a product with the same name has been deregistered in Malaysia since Jan 2005. This illegal product is not a listed Chinese proprietary medicine with HSA and not likely to be sold locally in the retail outlets.

Self-medication with complementary medicines adulterated with potent pharmaceutical drugs can lead to serious health risk. Healthcare professionals are reminded to enquire about complementary medicine use in their patients and are encouraged to report any serious adverse drug reactions to the Pharmacovigilance Unit of HSA.
Black cohosh (Cimicifuga Racemosa) & hepatotoxicity

Black cohosh (Cimicifuga racemosa), a perennial plant that is native to North America, is generally used to assist in the relief of the symptoms of menopause and is available as herbal health supplements. Based on the experience reported from overseas, it has become more widely used as women seek an alternative to hormone replacement therapy. However, the efficacy and long term safety of black cohosh is not clear.¹

Liver toxicities reported overseas
The Australia Therapeutics Goods Administration (TGA) recently reviewed the safety of black cohosh following reports of liver toxicities suspected to be associated with its use. As of Apr 2006, the TGA is aware of 49 cases of hepatotoxicity with black cohosh worldwide, including 11 Australian reports. These include cases of autoimmune hepatitis, massive and sub-massive necrosis. Serious cases have been reported to occur with use of less than a month.² In Australia, four patients were hospitalised, including two patients who required liver transplantation.³

According to TGA’s assessment, many of the reports were confounded by the use of other medications and the range of ingredients in the herbal formulation being used. However, the lack of other identifiable causal substance and exclusion of viral infection in the serious cases suggest a causal association between black cohosh and serious hepatitis.² TGA also observed that the incidence of liver reaction is very low considering the widespread use of black cohosh. Following the safety review, the TGA has strengthened the labelling of products containing black cohosh to state that black cohosh may harm the liver in some individuals and that it should be used under the supervision of a healthcare professional.

As of 31 Mar 2005, the UK Medicines and Health Regulatory Agency (MHRA) had received 20 reports of liver reactions suspected to be associated with black cohosh. The cases ranged in severity from abnormal liver function to various forms of hepatitis. The patients generally recovered or were reported to be recovering after stopping black cohosh.⁴ The mechanism for hepatotoxicity with black cohosh is not known. However, an immunological response has been suggested.⁵ Due to the limited information available about the formulation and usage of black cohosh in the UK as the majority of products on the market appeared to be unlicensed herbal remedies, the agency is currently keeping the safety of black cohosh under review.

Local experience
HSA has not received any local reports of hepatotoxicity associated with black cohosh. Healthcare professionals are encouraged to obtain a thorough medication history from patients presenting with hepatic dysfunction including their use of alternative medicines, including herbal and other complementary medicines, as well as alcohol and conventional medicines. Healthcare professionals are also encouraged to report suspected adverse reaction to complementary medicines to the Pharmacovigilance Unit of the HSA.

References

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