The Health Sciences Authority (HSA) and its Pharmacovigilance Advisory Committee (PVAC) have recently reviewed the safety profile of promethazine in children following the action taken by the US Food and Drug Administration (FDA) to contraindicate the use of promethazine hydrochloride preparations (e.g. Phenergan®) in children younger than 2 years old.

From our review of the risks versus benefits of promethazine, it was concluded that the risk of serious adverse drug reactions outweighs the potential benefits of the drug in young children. To reflect this safety concern, HSA is currently working with pharmaceutical companies to include the following information in the affected package inserts/patient information leaflets:

- Promethazine is contraindicated in children less than 6 months old;
- It is not recommended for use in children less than 2 years old;
- Caution should be exercised when used in children 2 years of age and older.

Summary of HSA’s review
Promethazine containing preparations are widely used in children for their antihistamine, antiemetic, and sedative properties. Since its approval in the US in 1951, serious and life-threatening adverse events have been reported with promethazine when used in children. Between the period 1969 – 2003, there were 125 cases of serious adverse events reported in patients below 17 years of age. These include respiratory depression, apnoea, cardiac arrest, seizures, dystonic reactions and hallucinations. For the cases involving respiratory depression (38 reports), about 57% occurred in young patients between 1.5 months - 2 years old. Based on the US FDA’s analysis, respiratory depression occurred over a wide range of doses (0.45 mg/kg - 6.4 mg/kg of promethazine).

Another point highlighted by the US FDA was that serious outcomes such as death, disability, life-threatening events, and hospitalisation occurred with all routes of administration (oral, rectal and parental).

A review of the product information of promethazine containing preparations in countries such as the UK and Australia showed they contain cautionary statements on the use of promethazine in young children. For instance, the product information of promethazine containing elixirs carries the precaution that the product is not recommended for children under 2 years of age.

Conclusion
Although there have been no local reports of fatal ADRs associated with promethazine, HSA is aware of cases of apnoea occurring in very young children. In view of the unpredictable nature of the adverse events and their serious outcomes, healthcare professionals should exercise caution when prescribing promethazine to young children.
Adverse Drug Reaction news

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Topical immunomodulators for treatment of atopic dermatitis

The US FDA has issued a public health advisory to inform healthcare providers of potential safety concerns associated with Elidel® and Protopic®.

Pimecrolimus cream (Elidel®, Novartis) and tacrolimus ointment (Protopic®, Johnson & Johnson) are the 2 topical immunomodulators which were granted local marketing approval in January 2003 and March 2004 respectively.

Mechanism of action

The exact mechanism of action of these drugs in atopic dermatitis (eczema) is not known. However, it has been shown that they inhibit T-cell activation and release of various cytokines (e.g. interleukins and interferon gamma).

Although these products are applied topically, low serum levels of the drugs (<2.0 ng/mL) have been detected in some patients and more frequently in children. This observed higher systemic exposure in children may be related to their greater body surface area to mass ratio.

Development in the US

Topical immunomodulators are increasingly being used in the US as first-line therapy in atopic dermatitis because they are perceived to be safer than steroid preparations. This perception of physicians and patients has been attributed to aggressive promotion of the drugs in the US market.

Prompted by concern over the increasing use of these products especially in very young children and findings of carcinogenicity in some of the animal studies as well as post-marketing reports of malignancies, the US Food and Drug Administration (FDA) issued a public advisory in March 2005. In its advisory, the FDA reminded healthcare professionals that these drugs had not been approved for use in children younger than 2 years of age. It also advised that they should be used for short periods of time and should not be used in patients who are immunocompromised.

As requested by the US FDA, the manufacturers will be conducting further research to determine the carcinogenic potential of these drugs in humans.

HSA’s assessment

In view of the development in the US, HSA and its Pharmacovigilance Advisory Committee (PVAC) have reviewed the following safety information available:

i) Animal studies

The carcinogenicity findings were not uniformly detected in all animal studies. Although some animal studies revealed no carcinogenic potential, others demonstrated some signals. For studies with positive findings, the data showed that the risk of cancer increased with increasing dose and duration of treatment. It was noted that in general the doses used in these animal studies were higher than the maximum recommended human dose (MRHD). For example, lymphoma formation in mice was reported with dermal application of tacrolimus and pimecrolimus dissolved in ethanol, at 26 times and 47 times MRHD, respectively.

ii) Post-marketing reports

As of December 2004, the US FDA reported that it received 10 and 20 cases of post-marketing reports of malignancy-related events (e.g. lymphoma) with pimecrolimus and tacrolimus, respectively. For many of these cases, the causality could not be established due to the presence of other confounding factors. To date, HSA has not received any local reports of malignancy associated with pimecrolimus or tacrolimus.

Recommendations

HSA and its PVAC advise physicians to weigh the risks and benefits of the drugs for individual patients and to take into consideration the following:

- Pimecrolimus and tacrolimus are approved for short-term and intermittent treatment of atopic dermatitis in patients who are not adequately responsive to, or intolerant of other treatments;
- They are not approved for use in children younger than 2 years old. The long term effect of these drugs on the developing immune system is not known;
- They should not be used continuously for a prolonged period of time as their long-term safety have yet to be determined;
- Patients who are immunocompromised should not be prescribed pimecrolimus or tacrolimus.

References

1. FDA’s Paediatric Advisory Committee Meeting. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm
Adverse Drug Reaction news

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Capecitabine (Xeloda®, Roche) is a cytostatic agent indicated for metastatic breast cancer when used as an adjunct to docetaxel, and for metastatic colorectal cancer.

The co-administration of capecitabine and warfarin may predispose a patient to an increased risk of bleeding. The probable mechanism for the interaction is the down-regulation of the CYP 2C9 isoenzyme by which warfarin is principally metabolised.

Post-marketing reports have revealed clinically significant increases in prothrombin time (PT) and the international normalised ratio (INR) in patients who were stabilised on anticoagulants when capecitabine therapy was initiated. These events occurred within several days to several months after concurrent therapy.

**Overseas case reports**

In 4 patients with cancer, chronic administration of capecitabine (1250 mg/m² 2 times daily) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 91%.

A 91-year-old woman was prescribed a 2.5 mg/day dose of warfarin with target INR of 2-2.5 while concurrently receiving capecitabine for rectal adenocarcinoma. After 2 cycles of capecitabine, she was admitted to the hospital with a PT of 72.9 and INR >10.

Another 72-year-old woman received 2.5 mg/day of warfarin with target INR 2-3 for pulmonary embolism. She subsequently received capecitabine 8 months later, and was admitted to the hospital with a PT >100 and INR >10 after 2 cycles of capecitabine.

**Recommendations**

Patients who are prescribed warfarin and capecitabine concurrently should be closely and regularly monitored for alterations in the PT or INR; the dose of warfarin should be re-titrated if necessary.

References


1. Dinoprost (Prostin E2, Pfizer)

Preparations that now come under contraindications include: multiple gestation, grand multiparity, engagement of the head trot taken place, previous uterine surgery, cervical incompetence or dilatation, basal heart rate pattern suggesting incipient foetal compromise or other coexisting conditions where either maternal or foetal benefit/risk ratio becomes surgical intervention, unexplained vaginal discharge (for abnormal uterine bleeding during current pregnancy & nonviable presentation.

Under special warnings/precautions, women >50 yrs with complications during pregnancy & those with gestational age >40 who have been shown to have an increased risk of post-partum disseminated intravascular coagulation, which may further increase the risk associated with labour induction. Caution should be exercised when using dinoprostone in these women as measures are applied to detect an evolving fibrinolytic as soon as possible post-partum.

Under interactions, it has been added that a dosing interval of at least 6 hours is recommended in the sequential use of oxytocin following dinoprostone. Concomitant use with other oxytocic agents is not recommended.

2. Drospirenone & ethinylestradiol (Yasmin®, Schering AG) Yasmin® is contraindicated in severe hyper tension, severe dyslipoproteinemia, cholestatic jaundice, pregnancy or history of jaundice associated with use of the pill. Serum levels of drospirenone vs controls were 37% higher in women with moderate renal impairment, & levels of drospirenone vs controls were 37% higher in women with moderate renal impairment, & comparable between women with mild renal impairment respectively. Additionally, mean exposure to drospirenone in moderate liver impairment is about 2.5 times the exposure in normal liver function.

3. Etoricoxib (Arcoxia®, MSD) The duration for treatment of acute gouty arthritis is limited to a maximum of 8 days. Warnings on possible increased cardiovascular effects associated with selective COX-2 inhibitors have not been adequately controlled.

New list of contraindications have been included: (1) patients with congestive heart failure (NYHA II-IV); (2) patients with established ischemic heart disease; (3) patients with severe autoimmunoe disease (including patients who have recently undergone coronary artery bypass graft or angioplasty); (3) patients with hypertension whose blood pressure has not been adequately controlled.

4. Felodipine (Plendil®, AsthmaZenea) Felodipine may increase the concentration of tacrolimus & concurrent use should therefore be avoided.

5. Fosaprin (Monfrugy, Bristol-Myers Squibb) A new warning states that reversible intestinal perforation has been reported rarely in patients treated with ACE inhibitors.

6. Gadopentetic acid, dimeglumine salt (Magnesvir®, Schering AG) The maximum utilisation of IV injection dose for cranial & spinal MRI for adults is 0.6 mL/kg. The maximum dose for whole body MRI is 0.6 mL/kg for adults & 0.4 mL/kg for children. Patients should refrain from eating 2 hours prior to investigation to reduce aspiration risk. Sedation may be required in excitable & anxious patients as these conditions may increase the risk of adverse effects.

Precautions added include: history of bronchial asthma or other allergic disorders; patients with cardiology disease. Patients taking beta-blockers may be resistant to effects of beta agonists. Patients with severe disorders or intracranial lesions may be at increased risk of respiratory arrest when given Magnesvir. In severely impaired renal function, the benefits must be weighed against risks before use.

7. Ganimel (Ogralutafen, Organon) A new special warning has been added: the incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conceptions. The use of GFRUH antigens during ART is not found to be associated with an increased risk of congenital ACHTER.

8. Immune globulin intravenous (Gammagard S/D®, Baxter) New precautions added VIGG can cause blood group antibodies & cause positive direct antiglobulin reaction & rarely haemolysis.

There have been reports of noncardiovascular pulmonary oedema (Transmission Related Acute Lung Injury [TRALI]) in patients administered VIGG; characterized by severe respiratory distress, pulmonary oedema, hypoxemia, normal left ventricular function & fever. It typically occurs within 1-6 hours after transfusion.

Appropriate laboratory tests are required if: signs or symptoms of haemolysis are present after VIGG infusion; TRALI is suspected; patient is at risk of hyperviscosity. It has been added that patients at risk may include those with a history of arteriosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, &/or known or suspected hyperviscosity, hydropoagulable disorders & prolonged periods of immobilisation.

9. Medroxyprogesterone (Farlutal®, Pfizer) Farlutal® is contraindicated in known or suspected pregnancy & patients with undiagnosed vaginal bleeding. Under warnings & precautions, it is stated that medroxyprogesterone may cause some degree of fluid retention & that it may decrease the levels of some estrogen biomarkers such as plasma/urinary steroids, gonadotrophs & sex hormones binding globulin.

Patients receiving medroxyprogesterone may exhibit suppressed adrenal function & have decreased ACTH & corticosteroid blood levels. Additionally, the use of medroxyprogesterone in oncology indications may cause partial adrenal insufficiency during metypaone testing. It is recommended that patients take adequate calcium & vitamin D as BMD decrease (reversible) has been demonstrated in women given medroxyprogesterone intramuscularly.

10. Methylprednisolone (Solu-Medrol®, Pfizer) Some new special warnings include possible cardiac arrhythmias, circulatory collapse, cardiac arrest following rapid administration of large IV doses of methylprednisolone. Bradycardia has also been reported with large doses. Euphoria, insomnia, mood swings, personality changes & severe depression to dark psychotic manifestations may occur. Existing emotional instability or psychotic tendencies may be aggravated.

Acute myopathy has been reported in patients with disorders of neuromuscular transmission or patients receiving concurrent neuromuscular blocking drugs. Elevations of creatinine kinase may occur. Kaplan’s syndrome can occur in patients receiving corticosteroid therapy.

11. Oseltamivir (Tamiflu®, GSK) Some new special warnings include possible cardiac arrhythmias, circulatory collapse, cardiac arrest following rapid administration of large IV doses of oseltamivir. Bradycardia has also been reported with large doses. Euphoria, insomnia, mood swings, personality changes & severe depression to dark psychotic manifestations may occur. Existing emotional instability or psychotic tendencies may be aggravated.

Acute myopathy has been reported in patients with disorders of neuromuscular transmission or patients receiving concurrent neuromuscular blocking drugs. Elevations of creatinine kinase may occur. Kaplan’s syndrome can occur in patients receiving corticosteroid therapy.

12. Risperidone (Risperdal®, Johnson & Johnson) There is a new warning for use in elderly patients with dementia. Elderly patients with dementia treated with atypical antipsychotic drugs have increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotic drugs. In 2 out of 4 oral Risperidone placebo-controlled trials, higher incidence of mortality was observed in patients treated with risperidone plus anticholinergic compared to patients treated with risperidone alone.

Physicians should weigh the risks vs the benefits when prescribing antipsychotics to patients with Parkinson’s disease or dementia with Lewy Bodies since both groups may be at risk of neuroleptic malignant syndrome as well as increased sensitivity to antipsychotic medications.

13. Rosiglitazone (Avandia®, Glaxo) Avandia® should not be used if the patient has active liver disease. It is recommended that liver enzymes be checked prior to the initiation of therapy with Avandia® & periodically thereafter. Avandia® should not be initiated in patients with clinically evident liver disease or significantly increased baseline liver enzyme levels; & used with close monitoring in patients with mildly elevated liver enzymes.

14. Saguinar (Fortovase®, Roche) The following drugs are contraindicated with Fortovase®: ergot derivatives, amiodarone. The following drugs are contraindicated with loratine: Fortovase®, Fosinopril (Monopril®, AstraZeneca) & Fosinopril (Monopril®, Pfizer) For patients taking loratine-boosted Fortovase® as part of antiretroviral therapy due to the risk of severe hepatocellular toxicity observed in a drug-drug interaction. Coadministration with rifabutin or azithromycin could lead to significantly reduced plasma levels of saquinavir and thus should not be given with unboosted Fortovase® (Invirase®, Roche) (justbod to the above chart). Under special warnings and special precautions for use, patients with rare hereditary problems of galactose intolerance, the Lapp deficiency or glucose-galactose malabsorption should not take these medicines.

15. Vestlateine (Elexor XR®, Wyeth) The safety & efficacy of venlafaxine therapy in combination with weight loss agents including phentermine has not been established, & hence not recommended.

Serum cholesterol & QT interval for Elexor XR® treated patients were increased relative to placebo-treated patients.

In paediatric clinical trials, there were increased reports of hostility & especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation & self-harm. Increased appetite, weight loss, increased blood pressure, increased serum cholesterol, abdominal pain, agitation, dyspepsia, eycithomas, epistaxis & myalgia have been observed in children ≥6 yrs of age.

16. Vigabatrin (Sabril®, Aventis) Under special warnings, besides undergoing systematic visual field examination when starting vigabatrin & at regular intervals, visual field testing should continue every 6 months for the whole duration of treatment.

For safety-related product labeling amendments, you can refer to http://www.hsa.gov.sg/cda/labelchanges
GlaxoSmithKline (GSK) have recently issued a Dear Healthcare Professional letter to notify our healthcare professionals of the preliminary findings of a retrospective epidemiological study which showed a 2-fold increase in the risk of congenital malformations in infants born to mothers who took paroxetine during the first trimester compared to other antidepressants.

Paroxetine (Seroxat®) is indicated for the treatment of depression, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder and post-traumatic stress disorder. Seroxat CR® is approved for the treatment of major depressive disorder. The company has updated the package inserts of both Seroxat® and Seroxat CR® to reflect this risk under the Pregnancy subsection.

**Background**

The study, initiated by GSK was conducted in 3,581 pregnant women. Preliminary analysis showed that infants of mothers who were given paroxetine in the first trimester of pregnancy have a 2.2 fold increase [adjusted odd ratios of 2.2 (95% CI: 1.34-3.63)] for congenital malformations as a whole and a 2.08 fold increase [2.08 OR (95% CI: 1.03-4.23)] for cardiovascular malformations alone. Majority of the cardiovascular malformations reported were ventricular septal defects. The prevalence of congenital malformations as a whole and cardiovascular malformations alone were approximately 4% and 2%, respectively. This study did not include a comparison to infants who were not exposed to any antidepressant. Therefore, these data should be viewed in the context of the overall prevalence of congenital malformations within the general population, which is estimated in the US to be approximately 3% for any malformation and approximately 1% for cardiovascular malformations alone.1

Other independent studies conducted earlier on pregnancy outcome following first trimester exposure to selective serotonin reuptake inhibitors (SSRIs), including paroxetine, have not provided evidence for an increased risk of major malformations with these medications. Additional epidemiology studies would need to be conducted to more fully understand these preliminary findings.

**Recommendations**

Physicians are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy and to discuss the risks and benefits as well as treatment alternatives with their patients. Paroxetine should be used during pregnancy only if the potential benefit outweighs the possible risk to the foetus.

**Addendum**

The workgroup of the MOH Clinical Practice Guidelines on Depression would like to refer healthcare professionals to a statement on page 17 of the guidelines which states that “In pregnancy and nursing mothers, the relative risks and benefits of using antidepressants must be carefully weighed. There is no evidence of increased risk of teratogenesis or spontaneous abortions following exposure to antidepressants such as tricyclic antidepressants and SSRIs in early pregnancy.” The workgroup would like to advise all healthcare professionals that this statement might no longer be valid in the context of the current information available on paroxetine.

**References**

1. GSK Clinical Trial Register; http://ctr.gsk.co.uk/Summary/paroxetine/epip083.pdf
Suicidality risk associated with atomoxetine

New safety data regarding the use of atomoxetine to treat attention deficit hyperactivity disorder in children and adolescents

Atomoxetine (Strattera®, Eli Lilly and Company) a norepinephrine re-uptake inhibitor, is licensed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, in adolescents and adults. It was registered in Singapore in April 2005.

Reanalysis of trial data

Eli Lilly and Company has issued a Dear Healthcare Professional Letter to alert our healthcare professionals of an increased risk of suicidal thinking in children and adolescents associated with the use of Strattera®.

This new finding emerged as part of a larger evaluation of psychiatric drugs and suicidality following the US Food and Drug Administration’s request to manufacturers to conduct a review of their database and clinical trials.

Eli Lilly and company reanalysed 12 clinical trials on Strattera® conducted in children with ADHD and 1 trial in children with enuresis. The review involved more than 2,200 patients, including 1,357 receiving Strattera® and 851 receiving placebo. The analysis showed a greater risk of suicidal thinking during the first few months of treatment in those receiving Strattera®. The average rate of suicidal thinking was about 0.4% in children treated with Strattera® compared to no events in children treated with placebo. There was 1 suicide attempt in these 2,200 patients which occurred in a patient on Strattera®. A similar analysis in adult patients treated with Strattera® for either ADHD or major depressive disorder found no increased risk of suicidal ideation or behaviour with the use of Strattera®. There were no completed suicides among children, adolescents, or adults on the medication during any Strattera® clinical trials.

Recommendations

Physicians are advised to carefully monitor patients on Strattera® for possible clinical worsening, as well as agitation, irritability, suicidal thinking or behaviours, and unusual changes in behaviour, especially during the initial few months of therapy or when the dose is increased or decreased. Patients, their families and caregivers should be informed of this risk. They should also closely observe the patient for signs and symptoms and communicate these to the physicians should they occur.