



MALAYSIAN ADVERSE DRUG REACTIONS NEWSLETTER

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A STUDY OF ADVERSE DRUG REACTIONS IN MALAYSIAN CHILDREN REPORTED TO NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB), MINISTRY OF HEALTH MALAYSIA

Purpose : To evaluate the frequency, seriousness and outcome of adverse drug reactions (ADR) encountered in pediatric patients, to describe the trend for the drugs most frequently suspected to cause the ADRs and the various types of ADRs reported using data obtained from the Adverse Drug Reaction Monitoring Program in Malaysia.

Method : Data from ADR reports submitted to the National Pharmaceutical Control Bureau (NPCB) were collected from the database Quest2 and analyzed for the period from 2004 until 2005 (24 months).

Results : Throughout the period of 2004 – 2005, NPCB received a total of 4041 ADR reports from various age range. After extracting all the reports for patients aged below 12 years, a total of 432 (10.7%) reports were analyzed. The highest number of reports involved the age range of 1 month to 3 years i.e 222 cases (51.4%) The number of drugs suspected to cause the ADRs was 499 drugs (1.1 drugs/patient) and a total of 699 (1.6 ADRs/patients) ADRs were identified.

There were 60 reports (13.9%) where the ADR was reported to be serious but the majority of ADRs, 41.9%, were reported to be moderate and 34.9% were mild in

nature. Another 9.3% were unknown.

A total of 298 patients (69.9%) recovered from the ADRs and 5 patients (0.3%) were suspected to have had drug related deaths. 19.9% of the cases had not yet recovered at the time of reporting and the outcome of patients was unknown in 9.9% of the reports.

Out of the 499 drugs suspected to cause the ADRs, 197 (39.5%) were antibiotics followed by vaccines (18.6%). The clearly most frequently reported reactions involved the skin and appendages disorders (45.9%) followed by general disorder (15.8%) and central and peripheral nervous system disorders (14.8%).

Conclusion : Although the number of cases involving the paediatric population which suffered from ADR is small compared to the total number of ADRs reported, more investigations need to be done in order to identify risk factors which may have contributed to the occurrence of these ADRs. In respect to that, the National Adverse Drug Reaction Monitoring Program represents a valuable hypothesis generating tool in evaluating the characteristics of ADRs occurring in the paediatric population.

ISSUES OF CURRENT INTEREST

5-HYDROXYTRYPTAMINE RECEPTOR AGONISTS (TRIPTANS) SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) SELECTIVE SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS) SEROTONIN SYNDROME

FDA notified healthcare professionals and consumers of new safety information regarding taking medications used to treat migraine headaches (triptans) together with certain types of antidepressant and mood disorder medications namely selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs). A life-threatening condition called serotonin syndrome may occur when triptans are used together with SSRI or SNRI.

Serotonin syndrome occurs when the body has too much of a chemical found in the nervous system (serotonin). Each of the above medications (triptans, SSRIs, and SNRIs), cause an increase in serotonin levels. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhoea.

Physicians prescribing a triptan, SSRI or SNRI should:

- Keep in mind that triptans are often used intermittently and that either the triptan, SSRI or SNRI may be prescribed by a different physician

- Weigh the potential risk of serotonin syndrome with the expected benefit of using a triptan with an SSRI or SNRI
- Discuss the possibility of serotonin syndrome with patients if a triptan and an SSRI or SNRI will be used together
- Follow patients closely if a triptan and an SSRI or SNRI are used together, particularly during treatment initiation, with dose increases, or with the addition of another serotonergic medication
- Instruct patients who take a triptan and an SSRI or SNRI together to seek medical attention immediately if they experience the symptoms of serotonin syndrome (described above).

Patients taking a triptan along with an SSRI or SNRI should talk to their doctor before stopping their medication and should immediately seek medical attention if they experience any of the above symptoms. FDA requested that all manufacturers of triptans, SSRIs and SNRIs update their prescribing information to warn of the possibility of serotonin syndrome when these medications are taken together.

The SSRIs, SNRIs and triptans which are registered with the DCA are listed below.

SSRIs	SNRIs	Triptans
Cipram (<i>citalopram</i>)	Cymbalta (<i>duloxetine</i>)	Imigran (<i>sumatriptan</i>)
Luvox (<i>fluvoxamine</i>)	Effexor (<i>venlafaxine</i>)	Maxalt (<i>rizatriptan</i>)
Lexapro (<i>escitalopram</i>)		Relpax (<i>eletriptan</i>)
Seroxat (<i>paroxetine</i>)		
Prozac (<i>fluoxetine</i>)		
Zoloft (<i>sertraline</i>)		

The registration holders have been notified to include this new safety information in their product package inserts.

Ref : USFDA MedWatch Safety Alert, July 19, 2006.

INCOMPATIBILITIES CEFTRIAXONE AND CALCIUM

The French and Swiss Authorities, Afssaps and Swissmedic, have requested a label change to their national prescribing information texts to include a warning statement on possible adverse events with fatal outcome following concomitant use of Ceftriaxone (Rocephin) with Calcium or Calcium containing products.

Incompatibilities with solutions containing calcium have been known for several years and are described in product label under the section on "Warnings and Precautions".

From the adverse events database in Roche Headquarters, a total of five relevant cases could be identified which are fatal

adverse event reports. One case was reported in France in 2002 and the other four occurred more than 10 years ago.

Incorrect administration can be assumed to have played a causal role in four cases. In the remaining case, the cause of death could not be clarified. Crystalline embolic material was found in two cases. All patients were suffering from severe underlying conditions which might have caused or at least significantly contributed to the fatal outcome.

All health professionals have to bear in mind not to use Ceftriaxone together with Calcium or Calcium containing products.

- Ref : 1. Rocephin Drug Safety Reports N.1023755
2. Swissmedic : Information For Health Professional
Available at <http://www.swissmedic.ch>

POSSIBLE SIGNAL OF DEPRESSION WITH EZETIMIBE.

Since Ezetimibe (Ezetrol) was registered in Australia in June 2003, ADRAC received 265 reports associated with the used of this drug. 12 of the reports describe depression or depressed mood in patients aged between 60 to 82 years.

According to ADRAC's assessment the unusual feature in these cases was the fast onset of the symptoms which is between 4 days in seven reports and 4-6 weeks in three reports. In one of the reports, symptoms resolved after the dosage was decreased from 10mg to 5mg.

Another report described exacerbation of pre-existing depression after the second dose of Ezetimibe.

5 of the patients abated from the symptoms after withdrawal of the ezetimibe, but recurred on rechallenge. In addition, 4 patients recovered after stopping ezetimibe and a further

patient was recovering with antidepressant therapy after ezetimibe withdrawal.

The Ezetrol Product Information does not mention depression as a finding in clinical trials of this drug (1), but according to ADRAC, "the pattern of reporting suggests a possible causal association between ezetimibe and depression, particularly in elderly patients in the early phase of treatment". (2)

MADRAC received one report of a 30 years old female patient, diagnosed with high cholesterol who was placed on therapy with ezetimibe 10mg. After a month of treatment, she experienced depression, insomnia and crying in the middle of the night. Ezetimibe treatment was discontinued and the patient recovered from the experienced reactions. The reporter also felt that the reaction was related to the ezetimibe therapy.

1. Ezetrol Local Product Circular (LPC – EZE-T-112005i – Malaysia)
2. Australia Adverse Drug Reaction Advisory Committee,
Ezetimibe and Depression – a possible signal. Australian Adverse Drug Reactions Bulletin 25 : 19, No. 5, Oct. 2006

APROTININ INJECTION - TRASYLOL®

Two articles published in January 2006 reported the results of two new safety studies of Trasylool which indicated a higher risk of death and serious and/or life – threatening renal and cardiac adverse events following treatment with Trasylool.

Based on these findings, FDA Alert has highlighted the important revisions to the full prescribing information for Trasylool.

The new labeling for Trasylool has now a more focused indication for use only in patients who are at increased risk for blood loss and blood transfusion in association with cardiopulmonary bypass in the course of coronary artery bypass grafting. It should be administered only in the perioperative setting where cardiopulmonary bypass can be rapidly initiated.

A new warning about renal dysfunction where Trasylool administration will increase the risk for renal dysfunction and may increase the need for dialysis in the perioperative period has been added to the package insert.

Anaphylactic reaction, including fatal reactions, is one of the important risks associated with Trasylool administration. As a consequence of the higher risk for anaphylactic reactions, administration of Trasylool to patients with known or suspected exposure during the past 12 months is contraindicated.

The DCA has directed the product holder in Malaysia to update and include the relevant changes accordingly.

- Ref : US FDA – Information for Healthcare Professional

LOCAL CASE REPORTS

SWITCHING FROM RITALIN TO STRATERRA : SUSPECTED ASSOCIATION WITH PRIAPISM.

A 10 year old boy developed sexualized behavior after switching from Ritalin to Strattera in January 2006. He was found to be sexually abusing (pulled down pants and fondled genitalia of) an 8 year old boy on numerous occasions in the school bus. He had been taking 40mg Strattera daily for about 4 months for attention deficit hyperactive disorder (ADHD) and was also on Haloperidol for Tourette's syndrome. Previously, while he was

on Ritalin for the same indication, no similar reactions were observed. After these incidents, he was switched to Concerta. Sexualized behavior is not labeled in the product leaflet nor are there such reports in the WHO database. However, there are 21 reports of priapism attributed to the use of Strattera in the WHO database.

LENOGASTRIM AND FATAL ACUTE MEGAKARYOBLASTIC ANEMIA

A 17 year old girl, with severe congenital neutropenia (Kostman's Syndrome) was treated with daily prophylactic subcutaneous granulocyte colony-stimulating factor (G-CSF) from the age of eight to sixteen. Because of poor haematological and clinical response, the G-CSF was discontinued. Seven months after cessation of G-CSF therapy, she was noted to have an abnormal blood count. Bone marrow examination showed depressed erythropoiesis and granulopoiesis. A diagnose of acute megakaryoblastic leukemia was made and she underwent chemotherapy treatment. Unfortunately she died of sepsis during induction of chemotherapy.

A contributory role of Lenogastrim in this case cannot be excluded. It has been reported that the mortality rate is 70% within the first year of life in the absence of medical intervention. The patient's underlying immunosuppressive condition could explain the fatal outcome. However, the role of lenogastrim in the pathogenesis of malignant transformation to AML is complicated. It is because patients with Kostman's Syndrome have an increased risk of developing acute myelogenous leukaemia or bone marrow disorder.

ANZAPINE AND INCREASED TOTAL WHITE BLOOD CELL COUNT

MADRAC received 2 reports of patients experiencing high total white blood cell counts after oral administration of generic Clozapine 100mg (Anzapine)

The first case was a 39 year old female patient who was prescribed Anzapine 100mg Tablet to treat resistant schizophrenia. After 6 months, her laboratory investigations showed a raised total white blood cell level with high platelet and lymphocyte counts. The reactions subsided once the drug was discontinued and the patient was switched to Clozaril Tablet and subsequently recovered. The reporter felt that there is a possible relationship between the adverse reaction and the drug.

Similar reactions developed in the second case of a 27 year old male patient who had been on oral Anzapine 100mg for the last 5 months. The patient's total white blood cell count reduced slowly once the drug was stopped and switched back to oral Clozaril. Both patients were given the same dose of oral Anzapine, which is 150mg twice daily.

This adverse reaction is not listed in the product insert of Clozapine and MADRAC will continue to monitor this reaction since it is very specific to Anzapine.

CURRENT REGULATORY ISSUES

ACE INHIBITORS AND “INCREASED RISK OF BIRTH DEFECTS, FETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY”

Angiotensin-Converting-Enzyme (ACE) Inhibitors are contraindicated during the 2nd and 3rd trimester of pregnancy because of their association with an increased risk of foetotoxicity syndrome, but human data on their use in the 1st trimester is limited.

A recent study published in the New England Journal of Medicine, suggests that exposure to ACE Inhibitors during the first trimester of pregnancy cannot be considered safe and should be avoided. This cohort study included 29507 infants born between 1985 and 2000. 209 of the infants had been exposed to ACE Inhibitors in the 1st trimester, 202 infants with other antihypertensive agents during the 1st trimester and the rest were not exposed to any antihypertensive agents at any time.

The results showed that there was significant increased risk of major congenital malformation in infants whose mothers were exposed to ACE-Inhibitors.

Based on this study, the US FDA and Health Canada alerted healthcare professionals on this new safety issue, and requested that all ACE Inhibitors should carry a warning statement in their package inserts

In Malaysia, the Drug Control Authority has registered 110 products containing ACE inhibitors. To address this safety concern, the DCA at its 186th meeting, agreed to MADRAC's proposal that all ACE Inhibitors should carry the following warning statement in their package inserts:

“Increased risk of birth defects, fetal and neonatal morbidity and death when used throughout pregnancy”

ARGININE : A WARNING STATEMENT ON ‘NOT RECOMMENDED FOR PATIENTS FOLLOWING A HEART ATTACK’.

The Journal of the American Medical Association (JAMA) has published the results of a study on L-Arginine Therapy in Acute Myocardial Infarction (AMI). The study was investigating the possible benefits of L-Arginine on cardiovascular parameters following AMI but was stopped as a result of six deaths.

In view of the finding that arginine did not improve cardiovascular circulation after the first heart attack but could increase the risk

of death if used after a heart attack, Health Canada and TGA have decided that all L-Arginine products must carry a warning on their labels that reflects the current safety information.

In Malaysia, L-Arginine is classified as a health supplement and can be purchased easily over the counter. Therefore, the DCA at its 185th meeting agreed that the following warning must be included on the labels and package inserts of oral health supplement products containing L-Arginine:

“Arginine is not recommended for patients following a heart attack”

REPORTS FROM JOURNALS

THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT STUDY OF TAMOXIFEN AND RALOXIFEN (STAR) TRIAL.

JAMA has published the final results of the STAR trial, which compared raloxifene against tamoxifen for prevention of breast cancer in women at high risk. The STAR trial recruited 19,747 women with an increased five-year risk of breast cancer according to a standard model and they were randomized to treatment with either raloxifene or tamoxifen over five years.

The results showed no significant difference between the two groups in the incidence of invasive cancer (163 in the tamoxifen group versus 168 in the raloxifene group). Analysis of secondary outcomes found a lower incidence of non-invasive breast cancer in the tamoxifen group and a higher incidence of uterine cancer. However the numbers of events were small and

the differences were not statistically significant. Women in the raloxifene group had a lower risk of thromboembolic events, although the absolute risk in both groups was fairly low. Both treatments were generally well tolerated with limited impact on quality of life, although there were differences between the two in the pattern of symptoms that were reported.

They concluded that raloxifene has similar efficacy to tamoxifen in the prevention of invasive breast cancer in women at high risk, with a possible lower risk of thromboembolic events. Raloxifene may be a more acceptable option as a preventive drug but it is not clinically superior compared to tamoxifen.

Ref : JAMA vol 295, 2006

For any query, complaint and reporting adverse drug reaction, please contact:

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