



# DRUG ALERT

Regional Pharmacovigilance Centre (South)

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## REGIONAL PHARMACOVIGILANCE CENTRE (SOUTH)

Drugs are double edged weapons. They save several lives and at the same time they produce adverse effects ranging from mild skin eruptions to death. Many of these adverse effects will not be noticed during the clinical trials since the number of patients involved is relatively small. It was reported that about 51% of approved drugs had serious side effects that could not be detected prior to approval. One of the classical examples is that of fenfluramine and dexfenfluramine. About 31% subjects who took the above drugs showed heart valve abnormalities in echocardiographic investigations. Interestingly, fenfluramine was in the market for more than 24 years before this serious side effect was noticed. There are several similar examples such as liver damage from troglitazone, risk of seizure and dependency from tramadol, risk of aplastic anaemia from felbamate and blood disorders from temafloxacin. The latest examples are rofecoxib and valdecoxib. Further, some drugs are given accelerated approval (e.g., natalizumab) which compounds the problem of detecting adverse reactions. There is a need to have a strong pharmacovigilance program to monitor the adverse effects of drugs.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Recently, its concerns have been widened to include: herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. (WHO, 2002).

Realizing the importance of pharmacovigilance, Ministry of Health and Family Welfare, Govt. of India, with WHO funding, initiated a country wide National Pharmacovigilance Program. The program is co-ordinated by Central Drugs Standard Control Organization (CDSCO), New Delhi. The program was officially launched by the Honorable Minister of Health, Dr. Anbumani Ramadass at New Delhi, on November 23, 2004. CDSCO has established 2 zonal centres, 5 regional centres and 28 peripheral centres all over India.

The Regional Pharmacovigilance Centre (RPC) at JIPMER, Pondicherry co-ordinates the ADR monitoring in South India. Eight peripheral centres are attached to the RPC, JIPMER. The function of RPC

is to collect and analyse the ADRs reported from JIPMER and the eight peripheral centres. The RPC will carry out the "causality and severity assessment" and send a monthly report to the Zonal Centre. From the Zonal Centre the data will reach the database of CDSCO, New Delhi. The data from India will also be entered into the database of Uppsala Monitoring Centre (UMC, WHO), Sweden. This will help to distinguish the "signals" (first alert of a problem with the drug) from the background noise of routine ADRs reported and lead to regulatory decisions based on strength of the signals. The ADRs reported may serve to alert the prescribers, the manufacturers and the public to new risks of adverse drug reactions.

In order to facilitate quick submission of ADR reports, RPC, JIPMER has created a "webpage" at [www.jipmer.edu](http://www.jipmer.edu) for online reporting. This facility is the first of its kind in India. Besides, it also gives information about the peripheral pharmacovigilance centres attached to the RPC, the National Pharmacovigilance Programme and provides a hyper-link to CDSCO, New Delhi.

RPC, JIPMER has also started the publication of "Drug Alert", a monthly publication for providing drug information services to health professionals. It will also carry information about the important ADRs reported at RPC and also in the literature. This will also serve as a medium for expressing the views of health professionals for promoting the pharmacovigilance program.

After several unsuccessful fragmented efforts to monitor ADR at the national level, the present program was initiated in 2004. The success of this program depends on the co-operation of the health professionals in our country.

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## SELECTIVE COX-2 INHIBITORS : CURRENT STATUS

Selective COX-2 inhibitors, celecoxib and rofecoxib, were introduced in the year 1999. Many second generation COX-2 inhibitors viz., valdecoxib, parecoxib, etoricoxib and lumiracoxib were introduced subsequently. Data from the initial clinical trials indicated that COX-2 selective inhibitors have less gastrointestinal (GI) side effects than traditional NSAIDs but several serious and fatal cardiovascular adverse reactions were reported with these drugs in the following years.

The initial VIGOR trial (Vioxx Gastrointestinal Outcomes Research Study) with rofecoxib 50 mg/day for 9 months showed that the rate of GI events were 50% less than that of naproxen. However, a 5 fold increase in incidence of myocardial infarction was also observed. It was argued that this could be due to chance. When the APPROVe (Adenomatous Polyp Prevention On Vioxx) trial on rofecoxib found a significant increase (3.9 fold) in the incidence of serious thrombo-embolic adverse events, the seriousness of the side effects of rofecoxib were realized. The CLASS (Celecoxib Long term Arthritis Safety Study) trial with celecoxib 400mg BD was commonly cited as the strong evidence in the claims of celecoxib's superiority in terms of GI side effects over traditional NSAIDs. But its retrospective analysis also revealed the signs of increased cardiovascular risks.

In view of strong evidence, rofecoxib (Vioxx) was withdrawn by Merck in September 2004 and valdecoxib (Bextra) was withdrawn by Pfizer in April 2005.

A recent report on celecoxib published in WHO Pharmaceutical News letter (No.1, 2005, page 3) stated that M/s Pfizer stopped "Adenoma Prevention with Celecoxib (APC) trial" due to major cardiovascular events with celecoxib. This highlights the need to closely monitor the cardiovascular side effects of celecoxib.

The European Medicines Agency concluded that the available data show an association between the duration and dose of intake of COX-2 inhibitors and the probability of suffering a cardiovascular event. It also recommended several safety restrictions for their usage.

### ***Present status of COX – 2 inhibitors in India:***

Rofecoxib was removed from the Indian market, based on the recommendation of the National Pharmacovigilance Advisory Committee (NPAC). The NPAC has recently recommended to the Government that all valdecoxib formulations be removed from the Indian market. It also advised the ADR monitoring centres under National Pharmacovigilance Programme

to keep a special watch on the ADRs of celecoxib, parecoxib and etoricoxib.

### **Prescription Advice for the use of selective COX-2 inhibitors**

*(Committee for Medicinal Products for Human Use, Europe)*

- Patients with established ischemic heart disease or cerebrovascular disease should be switched over to alternative treatment.
- Before prescribing a COX-2 inhibitor, the balance of gastrointestinal and cardiovascular risk should be considered in all patients, especially for those with risk factors for heart disease and those taking low dose aspirin, for whom gastrointestinal benefit has not been clearly demonstrated.
- The lowest effective dose of COX-2 inhibitor should be used for the shortest necessary period. Periodic re-evaluation is recommended, especially for osteoarthritis patients who may only require intermittent treatment.
- Gastroprotective agents should be considered for patients switched over to nonselective NSAIDs.
- Etoricoxib treatment should not be initiated in patients whose hypertension is not under control. Careful monitoring of blood pressure is advised for patients taking etoricoxib.

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### **DRUGS UNDER PHARMACOVIGILANCE SCRUTINY OF DCGI, NEW DELHI**

1. Selective COX-2 inhibitors
2. Phenylpropanolamine
3. Analgin
4. Nimesulide
5. Rosuvastatin
6. Cisapride
7. Droperidol
8. Furazolidone
9. Sildenafil

## ADVERSE DRUG REACTIONS - "INTERESTING CASE REPORTS"

### 1. "Sildenafil causes esophageal symptoms"

Most of the adverse effects of sildenafil are due to vasodilation caused by selective inhibition of cGMP-specific phosphodiesterase type 5. Two recent reports stated that sildenafil can cause more problems than an occasional sustained and painful erection. The first report describes esophageal symptoms caused by sildenafil 100mg. It was found that 3% of the patients suffered esophageal symptoms such as dysphagia and odynophagia as it decreased the resting pressure of the lower esophageal sphincter. (*J Clin Gastroenterol.* 2005;39(7):643–644)

***Patients are recommended to avoid food within the first hour after taking sildenafil***

### 2. "Sildenafil and myocardial infarction"

The second report describes a 45-year-old man developing acute myocardial infarction without any past history of cardiac disease. He was admitted to the hospital with a 3-hour history of chest pain, nausea, and vomiting within 1.5 hr of taking sildenafil 100 mg. The patient had not yet had any sexual contact. Electrocardiographic evidence, creatine kinase and troponin elevations suggested acute myocardial infarction. The patient did not have any prior history of cardiac disease, and his only risk factor was that he was a smoker. He was not taking any medications. He received the sildenafil from a friend without undergoing any type of physical examination. He made a normal recovery after treatment for acute myocardial infarction. (*Hosp Pharm.* 2005;40(8):849)

### 3. "Gatifloxacin can cause severe hyperglycemia"

A 65-year-old woman with no history of diabetes, developed hyperglycemia, after taking gatifloxacin. She was admitted to the hospital with a one day history of abdominal cramps, nausea, and vomiting. Her blood glucose was 1,121 mg/dL (normal range 70 to 100 mg/dL). She had a history of high BP, transient ischemic attacks, hyperlipidemia and renal failure. The patient was receiving gatifloxacin 200 mg daily for 9 days empirically for bronchitis, which was started during a prior hospitalization. After admission, she responded well to an insulin infusion combined with subcutaneous doses of regular insulin. (*Ann Pharmacother.* 2005;39(7):1349–1352)

***Reports of hypoglycemia with other fluoroquinolones have been documented, but only***

***gatifloxacin is reported to cause severe hyperglycemia***

### 4. "Cabergoline-Related Severe Restrictive Mitral Regurgitation"

A patient with Parkinson's disease (74 years male) was initially treated with levodopa. On addition of cabergoline, he developed bilateral rales and edema in both legs. After investigations it was diagnosed to be mitral regurgitation and they excluded the possible known causes for this. All the features resembled that seen with ergot alkaloids, fenfluramine and carcinoid syndrome. As cabergoline is an ergot derivative with dopaminergic action they conclude that it is the most likely cause for this effect. This serious adverse effect is important to know since the drug is also being offered illegally through the internet for its action on prolonging the orgasm in men. (*N Engl J Med* 2005, 353;18)

***Remember to monitor the cardiac side effects when cabergoline is prescribed to elderly patients***

### 5. "Itch and skin rash from chocolate during fluoxetine and sertraline treatment".

A 46-year-old man was treated with fluoxetine (20 mg daily) for depression. Due to itch and skin rash fluoxetine was stopped but symptoms of depression returned and he was put on sertraline. There were no urticarial symptoms and there was improvement in depression. After two weeks the patient noted intense itching sensation in his scalp which later spread to other parts after eating a piece of chocolate cake. The patient himself reported a similar incident of consuming chocolate mousse dessert before the first episode. He never had any reaction to chocolate earlier. SSRI together with serotonin-containing chocolate has increased serotonin concentration to a level where 5-HT receptors system at the dermal and epidermo-dermal junctional area is affected. The authors conclude that there are patients who are sensitive to increase in serotonin concentration (caused by chocolate) due to high activity of serotonergic system at dermo-epidermal junction. (*BMC Psychiatry* 2004, 4 :36)

***Warn the patients about the possible skin reactions when chocolate is consumed with SSRIs***

***Dr.Ravindra Kumar and  
Dr.Vinod Thomas, Department of Pharmacology***

## REGIONAL PHARMACOVIGILANCE CENTRE (SOUTH), JIPMER, PONDICHERRY ADR REPORTS RECEIVED

Centre	No. of reports
Manipal College of Pharmaceutical Sciences, Manipal	327
JSS Medical College and Hospital, Mysore	215
Al-Ameen College of Pharmacy, Bangalore	170
Amritha Institute of Medical Sciences, Kochi	102
PSG Institute of Medical Sciences and Research, Coimbatore	92
JSS College of Pharmacy, Ootacamund	91
JIPMER, Pondicherry	84
Sri Devaraj Urs Medical College, Kolar	77
Annamalai University, Chidambaram	21
<b>Total:</b>	<b>1179</b>

### ADR REPORTS - SEVERITY WISE ADR DISTRIBUTION

Drug	No. of ADR reported	Death (%)	Life threatening (%)	Hospitalization (%)	Disability (%)	Minor (%)
Antimicrobials	339	3 (0.8)	5 (1.3)	75 (22.8)	6 (1.6)	250 (73)
NSAIDs	112	1 (0.7)	1 (0.7)	20 (16.4)	0	90 (82)
Cardiovascular drugs	110	0	1 (0.7)	20 (18.6)	0	89 (81)
Anticancer drugs	107	2 (1.5)	5 (5.1)	10 (9.5)	2 (1.5)	88 (82)
Endocrine drugs	89	1 (1)	1(1)	9 (10)	4 (4.5)	74 (83.5)
Antiepileptics	86	1 (0.9)	5 (4.7)	30 (34.9)	0	50 (59)
Other CNS drugs	80	0	2 (2.25)	18 (22.75)	0	60 (75)
Antiasthmatics	44	1 (2.3)	0	8 (18.2)	0	35 (80)
Anti-snake venom	26	3 (11.5)	9 (34.6)	0	0	14 (54)
Miscellaneous	186	2(1)	2 (1)	31 (16)	3 (1.5)	148 (80)
<b>Total (%)</b>	<b>1179</b>	<b>14 (1.2)</b>	<b>31 (2.5)</b>	<b>221 (19)</b>	<b>15 (1.3)</b>	<b>898 (76)</b>

### GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS

Regional Pharmacovigilance Centre, JIPMER, Pondicherry invites reports of all suspected adverse reactions to drugs and other medicinal substances, including herbals, traditional and complementary medicines, blood products, medical devices and vaccines.

#### REPORT EVEN IF:

- The drug is an established one and the adverse drug reaction is well known
- You are not certain the product caused adverse event
- You don't have all the details

#### WHO CAN REPORT:

Any health care professional (doctors including interns, residents, dentists, nurses and pharmacists)

**WHERE TO REPORT:** You can report online at [www.jipmer.edu](http://www.jipmer.edu) or send your reports to:

**Dr. C. Adithan, Coordinator**

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**Note:** If you are at JIPMER you can also use the yellow forms provided in wards.