



DRUG ALERT

Regional Pharmacovigilance Centre (South)

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Centre's Report

Adverse Drug Reactions Reported to Regional Pharmacovigilance Centre-South

The safety of the drug is an important concern for both the doctors and patients. The efficacy of the drug can be established by randomized, double blind controlled trials before the drug is approved by the regulatory authorities. But the safety can be assessed

Table 1. Adverse drug reactions reported to Regional Pharmacovigilance Centre - South.

Peripheral centre	Year			Total
	2005	2006	Jan-Mar 2007	
Annamalai Nagar	48	386	105	539
Bangalore	200	141	32	373
Coimbatore	121	111	30	262
Kochi	119	248	79	446
Kolar	86	143	31	260
Manipal	396	293	92	781
Mysore	595	542	102	1239
Ooty	150	182	27	359
Puducherry	128	200	42	370
Total	1843	2246	540	4629

Table 2. Causality assessment of the ADRs

Year	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ Unclassified	Unassessable/ Unclassifiable	Total
2005	48	1449	266	25	11	44	1843
2006	27	1509	492	12	149	57	2246
2007	7	359	125	0	34	15	540

only by monitoring a large number of people using the drug. So adverse drug reaction (ADR) monitoring forms an integral part of drug approval and the routine therapeutics. This need led to the development of pharmacovigilance - the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems.

The National Pharmacovigilance Programme was started in November 2004 by Central Drug Standard Control organization (CDSCO), Ministry of Health and Family Welfare, Government of India. JIPMER, Puducherry is the Regional Pharmacovigilance

Centre (RPC) - South and has eight peripheral centres attached to it.

RPC - South and its peripheral centres are actively involved in ADR monitoring. A total of 4629 ADRs

Table 3. Commonly reported adverse drug reactions

Drug	Total ADRs	Commonly reported ADR
Anti Tubercular Therapy	209	Hepatitis, Elevation of liver enzymes
Ciprofloxacin	168	Skin rash
Diclofenac	160	Epigastric pain
Phenytoin	133	Ataxia, Nystagmus
Ceftriaxone	101	Diarrhoea
Prednisolone	100	Skin rash, Hyperglycemia
Amoxicillin	91	Diarrhoea

are reported by us up to March 2007 (Table 1). Every year the number of ADRs reported is steadily increasing as more and more health care professionals are made aware of the need to report all ADRs.

After RPC - South receives the ADR reports, the causality assessment is done. Table 2 gives the causality assessment of ADRs received by RPC-South.

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These ADRs are sent to the Zonal Centre. Finally all ADR reports enter into the database of Uppsala Monitoring Centre, Sweden.

Antimicrobials (33.8%), CNS drug (16.1%) and NSAIDs (8.3%) are the most commonly reported ADRs in our centre. Among them antitubercular drugs rank the first place with 209 ADRs reported and hepatotoxicity is the commonly reported ADR (Table 3). The other reported drugs with more ADRs

are ciprofloxacin, diclofenac and phenytoin.

The activities of RPC - South helps to build a database of ADRs for the Indian population. It is the duty of every health professional to report all ADRs to ensure the availability and usage of safer drugs.

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Drug Profile

Exenatide - A New Incretin Mimetic

Introduction

Type 2 diabetes mellitus (DM) occurs as a result of decreased secretion of insulin or increased peripheral resistance to insulin. Intensive treatment with sulphonylurea and biguanides is associated with increased risk of hypoglycemia and obesity. These adverse effects can be overcome by a new drug called exenatide, which is an incretin mimetic.

Incretin hormones

Incretin hormones play an important role in insulin secretion following meals. Patients with DM show total loss of incretin effect.^[1] Hence incretin deficiency may be playing a contributory role in the pathogenesis of DM. There are two most important incretin hormones namely, GIP (glucose dependent insulinotropic polypeptide) and GLP-1 (glucagon like peptide - 1). GLP-1 is metabolised rapidly by an enzyme dipeptidyl peptidase IV (DPP IV) to an inactive metabolite. Hence GLP-1 cannot be used clinically, but its analogs resistant to metabolism can be used clinically.

Exenatide

Exendin-4, a peptide isolated from the saliva of Gila monster (*Heloderma suspectum*) shares some of the glucoregulatory actions of GLP-1 and is resistant to DPP IV. Exendin-4 enhances beta-cell mass, thus impeding or even reversing the progression of disease. Exenatide is the synthetic peptide of exendin-4 and is the first incretin mimetic to reach market.^[2]

Results of trials

Exenatide showed improved glycemic control in patients with DM on maximal effective dose of sulphonylurea monotherapy. Out of 237 subjects, for 33 subjects (41.3%) in 10 µg group and for 28 (33%) subjects in 5 µg exenatide group the HbA_{1c} reached 7% compared to a baseline of > 7%. Exenatide at a dose of 10 µg was associated with reduction in body weight which was attributed to nausea and reduced food intake. However nausea was only in first few weeks of treatment while weight loss was progressive

over the 30 weeks in subjects with/without nausea. There was a small reduction in LDL cholesterol and apolipoprotein B levels, but other lipid parameters were unchanged.^[3]

Dose and route of administration

Exenatide is given subcutaneously 60 minutes prior to morning and evening meals. It is initiated as 5 µg bd and can be increased to 10 µg bd after 1 month of treatment, seeing the response. It is recommended for patients on metformin or and sulphonylurea who have suboptimal glycemic control.^[4]

Adverse effects & Interactions

Adverse effects mainly include nausea (44%), vomiting, hypoglycemia, diarrhea, dizziness, headache. Of these nausea is self limiting in 15-30% of patients.

Since exenatide delays gastric emptying, drugs like lovastatin, digoxin and oral contraceptive pills are to be taken 1 hour prior.

Contraindications

Patients with creatinine clearance < 1.8 l/h (30ml / min); children; pregnant and lactating women.^[5]

Current status

It is approved in United States for DM who have suboptimal glycemic control with metformin or sulphonylurea.

Three related compounds - liraglutide, CJC-1131, and ZP10 - are in clinical trials. GLP-1-receptor agonists while reducing glycosylated hemoglobin levels as effectively as existing oral agents do prevent weight gain. Moreover, because these compounds may increase beta-cell mass, they might slow or reverse the progressive islet-cell deterioration characteristic of diabetes.

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New Therapy

New Vistas in Cancer Therapy - Temsirolimus

Renal cell carcinoma is one of the important causes of death in cancer patients. The prognosis of stage IV renal cell carcinoma has been dismal to a large extent with the five year survival rate ranging from 5% to 10%.^[1] Temsirolimus is a new class of drug approved by US FDA on May 30, 2007 for the treatment of advanced renal cell carcinoma.^[2] Temsirolimus, an inhibitor of mammalian target of rapamycin (mTOR). Disruption of mTOR signaling, affects cell division and suppresses production of proteins that regulate angiogenesis. Treatment-related adverse events of temsirolimus included mucositis, skin rash, pneumonitis, hypophosphatemia, hyperglycemia, thrombocytopenia, anemia, and elevated liver function tests.^[1,3]

A randomized phase III open labeled multicentred clinical study was done in 626 patients which had three arms: Interferon α (IFN) alone (n=207), temsirolimus 25 mg alone (n=209), or the combination of temsirolimus (15 mg) and IFN (n=210). Single-agent temsirolimus was associated with a significant improvement in overall survival (OS) when compared to IFN (hazard ratio 0.73 [95% CI: 0.58, 0.92]; p=0.0078). The median OS was 10.9 and 7.3 months for temsirolimus and IFN respectively. The combination of 15 mg temsirolimus and IFN did not result in a significant increase in OS when compared with IFN alone and was associated with an increase in multiple adverse reactions.^[3]

The recommended dose of temsirolimus is 25 mg once a week infused over 30-60 minutes. Pretreatment with antihistamines is recommended to avoid allergic reactions.

Sirolimus is the most potent metabolite of temsirolimus which also acts on mTOR as temsirolimus but has been used for prevention of kidney transplant rejection and in drug eluting stents to reduce restenosis after coronary artery stent placement. No data is available on the use of sirolimus for renal carcinoma.

Temsirolimus has emerged as the third of a series of drugs that have been approved by FDA in the last sixteen months for the treatment of advanced renal cell carcinoma. Earlier sorafenib and sunitinib were approved for the same indication. Both these drugs are tyrosine kinase inhibitors which serve to reduce tumor angiogenesis by acting on vascular endothelium derived growth factor receptor.

Thus a better understanding of the various pathways involved in tumor angiogenesis has provided a tremendous fillip in the discovery of new drugs for the treatment of advanced renal cancer, a malignancy that has by and large been resistant to traditional chemotherapy. However more evidence is needed regarding safety, efficacy and combined use of temsirolimus with the other anticancer agents used in renal cell carcinoma.^[4]

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New ADRs

FDA Issues Safety Alert on Rosiglitazone

Rosiglitazone was approved for use in type 2 diabetes in 1999 as monotherapy or in combination with metformin, sulfonylurea, or insulin. It is used with caution in patients with edema and is not used in those having heart failure. Liver function should be monitored periodically and the drug should be used with caution in patients with hepatic impairment.

Nissen and Wolski^[1] carried out a meta-analysis of randomized control trials of rosiglitazone which had a duration of 24 weeks. The end points were myocardial

infarction (MI) and death from cardiovascular disease. The incidence of MI and cardiovascular death were 0.6% and 0.3% respectively. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; p=0.03), and the odds for death from cardiovascular diseases was 1.64 (95% confidence interval, 0.98 to 2.74; p=0.06). This meta-analysis has several methodological limitations as acknowledged by the authors and reviewers. Hence

the possibility that the findings were due to chance cannot be ruled out.

Based on the above findings, the steering committee of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD), trial (NCT00379769)^[2] undertook an unplanned interim analysis of some of the cardiovascular end points in that trial. Rosiglitazone was associated with a small, nonsignificant increase in the risk of the primary outcome (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). For the fatal or nonfatal myocardial infarction outcome, the hazard ratio was 1.16 (95% CI, 0.75 to 1.81).

FDA has been monitoring several heart related adverse effects of rosiglitazone. FDA has updated its labeling for rosiglitazone on several occasions. The most recent labeling include a new warning about a potential increase in heart attacks and heart related chest pains.^[3]

FDA is carefully weighing several complex sources of data, some of which show conflicting results. FDA's analysis of all available data are going on. Pending questions include whether the other drug in the same class - pioglitazone has less, same or greater risks. FDA has convened an advisory committee meeting on July. 30, 2007 to discuss the cardiovascular ischemic and thrombotic risks of thiazolidinediones. Hence physicians should analyse the risks and benefits and alternative therapies for every patient before prescribing rosiglitazone.

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Quiz

Pharma Quiz -1

1. The following anticancer agents suppress bone marrow EXCEPT
A. Bleomycin B. Doxorubicin
C. Paclitaxel D. Etoposide
2. The new oral antidiabetic drug, sitagliptin is an
A. Analog of glucagon like peptide (GLP - 1)
B. Inhibitor of dipeptidyl peptidase - 4
C. Analog of amylin
D. Analog of glucagon
3. Esophageal erosions can be produced by
A. Alendronate B. Atrovastatin
C. Lithium D. Haloperidol
4. All the following are potassium channel openers EXCEPT
A. Nicorandil B. Minoxidil
C. Cromakalim D. Hydralazine
5. The opioid that can be given by sublingual route is
A. Pethidine B. Fentanyl
C. Pentazocine D. Buprenorphine
6. Ebstein's anomaly can be caused by
A. Lithium B. Carbamazepine
C. Digoxin D. Doxorubicin
7. All The following drugs cause changes in colour vision EXCEPT
A. Digoxin B. Voriconazole
C. Ethambutol D. Penicillamine
8. The drug which has the highest volume of distribution is
A. Thiopentone B. Chloroquine
C. Heparin D. Phenytoin.
9. The drug which inhibits its own metabolism is
A. Carbamazepine B. Secobarbital
C. Erythromycin D. Cyclosporine
10. Which of the following does NOT have post-antibiotic effect.
A. Aminoglycosides B. Fluoroquinolones
C. Quinupristin-dalfopristin D. Macrolides

First two correct entries will be given prizes.

Answers in the next Issue.

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