

Safety alerts on Rosiglitazone

P. Subish, M. I. Mohamed Izham, P. Mishra, P. R. Shankar

Department of Pharmacology, Department of Hospital and Clinical Pharmacy, Manipal College of Medical Sciences/ Manipal Teaching Hospital, Nepal.

Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia.

Correspondence to: P. Subish, Asst. Prof. Department of Hospital and Clinical Pharmacy, Manipal College of Medical Sciences/ Manipal Teaching Hospital, Nepal.

e-mail: subishpalaian@yahoo.co.in

Background: Safety alerts and withdrawal of newer drugs in a wide spectrum of patients have become a common phenomenon. Such events have occurred many times in the past. Certain examples include the COX 2 inhibitors, Nimesulide, Cisapride etc.¹ After a period, either the controversy dies or the drug gets withdrawn from the market. Developing countries mainly follow the lead of the developed giants in matters of drug marketing and withdrawal.

Safety alerts on Rosiglitazone: Rosiglitazone is a Thiazolidinedione derivative used in the management of Diabetes. The United States Food and Drug Administration (US FDA) has approved this drug for the management of type 2 Diabetes Mellitus (DM) as an adjuvant.² Recently there has been a lot of arguments regarding the safety of Rosiglitazone. A major safety concern was raised when a meta-analysis concluded that Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and the risk of death from cardiovascular causes.³

On 21st May 2007, the US FDA issued a safety alert regarding the cardiovascular safety of Rosiglitazone and advised patients taking Rosiglitazone, especially those who are known to have underlying heart disease or who are at high risk of heart attack to talk to their doctor about this new information as they evaluate the available treatment options for their type 2 diabetes.⁴ However, another group of investigators has commented on the potential weaknesses of the meta analysis.⁵

What does the evidence say regarding safety profile of Rosiglitazone? A retrospective cohort analysis (n=139) demonstrated that significantly more patients required

medical intervention for treatment of congestive heart failure (CHF) during the 6-month period after rosiglitazone was added to their insulin-containing drug regimen compared to the 6-month period before rosiglitazone was added to therapy.⁶

Another double-blind trial involving 224 patients with type 2 DM and CHF with New York Heart Association (NYHA) Class I or II, found that treatment with Rosiglitazone was associated with more cardiovascular events than placebo.⁷ Rosiglitazone is also known to cause other side effects such as lipid abnormalities and blood toxicity.

Are other thiazolidinediones safe? It is also important to note that such a problem of cardiovascular related effects is seen not only with rosiglitazone but also with other glitazones. Pioglitazone use has caused plasma volume expansion and pre-load induced cardiac hypertrophy. It is not recommended to be used in patients with NYHA class III and IV cardiac status.⁸

Pioglitazone increased the reported rate of heart failure compared to placebo in the PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events). The PROactive trial was a multicenter, international, prospective, double-blind study that followed patients with type 2 DM with prior macrovascular disease for an average of 34.5 months.⁹

Pharmacovigilance in Nepal: The concept of ADR monitoring and Pharmacovigilance is new to Nepal. However, the Department of Drug Administration (DDA), Kathmandu, which is the national drug regulatory authority, has taken steps to establish an ADR monitoring program. Recently, Nepal has been given full member status by the

Safety alerts on Rosiglitazone

Uppsala Monitoring Center, Sweden; the WHO Collaborating Center for International Drug Monitoring. The Ministry of Health and Population has designated DDA as the national center for ADR monitoring.¹⁰ At present, there are two regional centers which are active in Pharmacovigilance; one is at Manipal Teaching Hospital, Pokhara and the other at the Institute of Medicine, Tribhuvan University, Kathmandu. The ADR reports from these centers are sent to the DDA and from there to the Uppsala Monitoring Center, Sweden.

Implications of safety of Rosiglitazone for Pharmacovigilance in Nepal: Although there are several controversies regarding the safety of this drug, there is no information on the safety profile of this drug in Nepal. This drug has been approved by the DDA and is widely prescribed. The following questions still remain unanswered;

- What is to be done for the patients who are already on this drug?
- Is it a problem only with Rosiglitazone or even with other drugs of the same category like Pioglitazone which are also available in Nepal?
- What are the data on the basis of which these drugs were approved in Nepal?
- Were any safety measures taken by the 'Nepalese drug regulatory authority' regarding this new class of antidiabetic drugs?

While the answer for most of the questions are unavailable at this point of time, the responsibility now lies in the hands of Pharmacovigilance centers of Nepal to generate safety profile for use of this drug in the Nepalese population in general and informing physicians by reporting adverse drug reactions. A group of authors have already stressed upon the need for Pharmacovigilance in Nepal.¹¹ The controversy about Rosiglitazone further stresses the importance of Pharmacovigilance.

References

1. Khan SA, Rao PGM, Rodrigues GS, Rajan S, Heda A. From thalidomide to rofecoxib: Can we afford to wait and watch? *International Journal of Risk & Safety in Medicine* 2006; **18**: 219–30
2. Klasco RK (Ed): *DRUGDEX® System*. Thomson Micromedex, Greenwood Village, Colorado (Edition expires [6/2007]).
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356 (**24**): 2457-71
4. FDA News. FDA Issues Safety Alert on Avandia. Available on <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01636.html>
5. Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. *N Engl J Med* 2007 Jun 14; 356 (**24**):2457-71.
6. Marceille JR, Goins JA, & Soni R: Chronic heart failure-related interventions after starting rosiglitazone inpatients receiving insulin. *Pharmacother* 2004; **24**(10):1317-1322
7. Product Information: AVANDIA(R) tablets, rosiglitazone maleate. GlaxoSmithKline, Research Triangle Park, NC, 2006
8. Product Information: Actos(R), pioglitazone hydrochloride. Eli Lilly Company, Indianapolis, IN, 2001
9. Dormandy JA, Charbonnel B, Eckland DJ, et al: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366(**9493**):1279-1289
10. Drug Bulletin of Nepal. Vol 15: No 2, Dec 2004-March 2005. (Available at <http://www.dinon.org/publications/dbnvol16.pdf> . Assessed on September 12th 2005).
11. Mishra P, Palaian S. Withdrawal of rofecoxib- a wake up call for drug safety. *Kathmandu Univ Med J* 2004; **2**(4):360