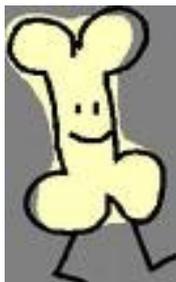


DRUG INFORMATION CENTER

PHARMA INFO-LINE

Does rosiglitazone (Avandia®) adversely affect the bone?

Rosiglitazone is an oral antidiabetic agent which acts primarily by increasing insulin receptors sensitivity and is used in the management of type 2 diabetes mellitus (DM), therefore it

improves glycemic control while reducing circulating insulin levels[1].

The drug is available in the Egyptian market with the brand name Avandia®, (GlaxoSmithKline) and the generic alternative, Rosizone®, (Apex-October Pharma), and both products are available as 4 mg tablets.

Generally rosiglitazone is well tolerated, it causes adverse effects that include; weight gain, upper respiratory tract infections, headache, and hypoglycemia. Fluid retention sometimes occurs and can lead to or exacerbate heart failure and pulmonary and general edema. Recently during post-marketing experience, rare cases of new-onset or worsening (diabetic) macular edema with decreased visual acuity have also been reported [2]. During the last few months a debate has been raised after the results of a meta-analysis that linked between the use of rosiglitazone and heart attacks (you can read the whole story in our newsletter, issue 6 June 2007). Eventually there is another adverse effect that has popped up, which is increased risk of bone fracture in women using rosiglitazone[3].

By the end of last year 2006 the results of the randomized double blind-control trial, ADOPT* were published [4],

the aim of which was to evaluate rosiglitazone, metformin and glyburide (known in Egypt as glibenclamide) in maintaining long-term glycemic control in type 2 diabetes. The study included 4360 patients with type 2 DM, and their only treatment was lifestyle management. Patients were randomly assigned to receive initial daily doses of 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide and then increased accordingly up to a maximum daily effective dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). The primary outcome was the time to monotherapy failure and all patients were treated for a median of 4.0 years. Patients with clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable / severe angina, known congestive heart failure (CHF, New York Heart Association class I, II, III, or IV), or uncontrolled hypertension were not included in the study.

The study analysis showed a significantly lesser cumulative incidence of monotherapy failure at 5 years with rosiglitazone (15%), compared either with metformin (21%), or glyburide (34%). This represents a risk reduction with rosiglitazone of (32%), as compared with metformin and (63%), as compared with glyburide.

This superiority of rosiglitazone was accompanied with significant increased risk of HF compared with glyburide, however the risk did not differ between rosiglitazone and metformin. Furthermore and this is

INSIDE THIS ISSUE:

[Stem cells & their therapeutic potential](#) 3

[Info-Alerts:](#) 4

-Do not switch your patient from one statin to another.

-Rocephin should not be mixed with calcium containing solutions.

Article summary

* ADOPT stands for Investigators in

A

D iabetes

O utcome

P rogression

T rial

our concern in this article; by examination of data on adverse events the authors had identified a higher rate of fractures in the group receiving rosiglitazone compared with the other two medications. (see table 1.)

results of the New Zealand study are "particularly compelling given the recent ADOPT results, showing a higher risk of fractures in diabetic women on rosiglitazone monotherapy compared with metformin or glyburide. They suggested that, despite the fact that the trial by

Grey *et al.* was conducted in healthy women, it is likely that the results will apply to women with diabetes also, given the increased rate of fractures noted in the ADOPT trial[6].

These findings made the company to ask an independent safety committee to conduct an interim analysis of

safety data for another large, ongoing trial of rosiglitazone; the results of the preliminary analysis were consistent with the ADOPT findings. The independent safety committee recommended that the second trial continue without modification; final results should be available in 2009, according to GlaxoSmithKline.

Eventually, GlaxoSmithKline warned in a 'DearHealthcare Professional' letter in both USA and Canada about the increased risk of fracture. You can read the letter at the link below;

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#rosiglitazone>.

Conclusion:

The clinical impact of these data on the prescribing trend in Egypt is still not known, anyway physician should consider the risk of fracture when initiating or treating postmenopausal female patients with type 2 diabetes mellitus with rosiglitazone.

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Table 1. Fracture incidence among patients of ADOPT

	Rosiglitazone	Metformin	Glyburide
	Number of patients (percent)		
Men	32 (3.95%)	29 (3.36%)	28 (3.35%)
Women	60 (9.30%)	30 (5.08%)*	21 (3.47%)*
Lower limb	36 (5.58%)	18 (3.05%) †	8 (1.32%)*
Upper limb	22 (3.41%)	10 (1.69%)	9 (1.49%) †
Spinal	1 (0.16%)	1 (0.17%)	1 (0.17%)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

This was an unexpected event, although it was not part of the pre-specified analysis plan of the trial, it left a big question mark. This adverse effect according to the analysis occurred mainly in women and it affected both the upper and lower limbs[4].

In order to determine whether rosiglitazone inhibits bone formation, a group of New Zealand researchers have conducted a randomized double-blind trial[5], in which fifty healthy, postmenopausal women (not diabetic) were either randomized to receive rosiglitazone 8 mg/d or placebo for 14 weeks. The primary end point was biochemical markers of bone formation, and secondary end points were a bone resorption marker and bone mineral density.

The osteoblast markers procollagen type I N-terminal propeptide and osteocalcin declined significantly in the rosiglitazone group compared with placebo group. These changes were evident by 4 wk and persisted for the duration of the study. There was no change in the serum B-C-terminal telopeptide of type I collagen, a marker of bone resorption. In addition, the total hip bone density fell in the rosiglitazone group compared with the base line; also the lumbar spine bone density fell significantly from baseline values in the rosiglitazone group but was not significantly different between groups. The authors concluded that short-term therapy with rosiglitazone exerted detrimental skeletal effects by inhibiting bone formation[5].

In an accompanying editorial, Ann V Schwartz and Deborah E Sellmeyer from the University of California, San Francisco, US, stated that the

Stem cells & their therapeutic potential

Stem cells are those cells that have been found at different stages of fetal development and are present in a wide range of adult tissues and have the following characteristics[1];

- The ability of self renewal.
- Proliferate through mitosis.
- Have capacity to proceed to various cell types under certain conditions by differentiation.

Historically, the Canadian professors Emeritus James Till and Ernest McCulloch about four decades ago (1960s) had laid the foundation for all current work on adult and embryonic stem cells, therefore they are called the fathers of the stem cells research. They revealed that a type of cell in bone marrow possesses the capacity to replicate itself and to differentiate to various lineages of mature blood cells [2].

Stem cells can be classified according to their source into[2]:

Embryonic stem cells; from the name it is obvious that we get it from the embryo, in particular from the inner cells at the earliest stage of embryonic development namely; the blastocyst.

Adult stem cells; also called somatic stem cells can be obtained from both adults and children, they occur in a wide variety of mature tissues and they are consequently classified into:

Blood Stem cells, these are the most studied type of adult stem cells and can be obtained from the bone marrow, circulating blood (peripheral blood), and umbilical cord blood.

Mesenchymal stem cells, are obtained from bone marrow stromal cells.

Neural stem cells, are isolated from adult brain and as well as from fetal brain tissues.

There is another classification that can be made according to their potential and cell types of their progeny into;

Totipotent stem cells, which is capable of giving rise to every cell type of the body and to form the whole body, the only example is the zygote.

Pluripotent stem cells, such as the embryonic stem cells can give rise to every cell type in the human body however is unable to form a functioning organism.

Multipotent stem cells, they can give rise only to a limited number of cell types, such as adult stem

cells, that is also called organ- or tissue- specific stem cells, and are found in specialized organs and tissues after birth.

The latter type (multipotent adult stem cells) has a primary function in the body; this is to replenish cells lost from normal turn over or disease in the specific organs and tissues in which they are found. The use of these cells in medicine is very tempting, however, the expectations and the claims such as "cure of all untreatable diseases" are to some extent exaggerated. However, there is a real possibility to utilize the characteristics of stem cells that is renewable source of tissues in medicine. Virtually many studies have been conducted in different fields of medicine to manage many difficult to treat diseases such as the blood stem cell transplant therapy, well known as bone marrow transplant therapy that has been proved to be beneficial for the treatment of patients with certain types of blood diseases and cancers[3]. It was only recently that some small-number studies have shown limited effect with scleroderma[4, 5], and some other pre-clinical and clinical studies have shown promising results in revascularization of ischemic tissues[6, 7].

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[READ IN THE NEXT ISSUE, OCTOBER 2007](#)

[STEM CELLS AND THERAPEUTIC NEOVASCULARIZATION; NEW HOPE IN PERIPHERAL ARTERY DISEASE](#)

INFO-ALERTS



Do not switch your patient from one statin to another!

Researchers evaluating data from the UK Therapeutic Health Informatics Network (THIN) primary care database have concluded that switching from atorvastatin to simvastatin

death or major cardiovascular events, and stroke, compared with not switching [see table 2]. Moreover, switch patients demonstrated non-significantly greater

Table 2. Cardiovascular risk for switch patients vs controls

Outcome:	Switch versus control	
	Hazard Ratio	P value
All-cause or major CV event	1.30	0.030
Major CV event	1.43	0.008
MI	1.36	0.258

therapy significantly increases the risk of death or major cardiovascular (CV) events; defined as myocardial infarction (MI), stroke or coronary revascularisation, a result which could have significant impact for policies that encourage switching from one statin to another.

A total of 2511 patients who were switched from atorvastatin to simvastatin, and 9009 controls who remained on atorvastatin, were identified in this study. Switching statin treatment was associated with significant increases in the risk of

risks of MI and coronary revascularisation than controls.

Patients who received atorvastatin for > 6 months were eligible for inclusion in this study. Those patients who switched to simvastatin were classified as 'switch', and were matched to < 4 control patients who remained on atorvastatin therapy.

Source:

Inpharma 1604 p. 6; 8 September, 2007.
European Heart Journal (2007) 28 (Abstract Supplement), 863

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INFO-ALERTS



Do not mix Rocephin® with calcium-containing products!

the US Food and Drug Administration (FDA) issued an alert highlighting revisions to the Contraindications, Warnings, and Dosage and Administration sections of the full prescribing information for Rocephin (ceftriaxone sodium) for Injection. The drug's manufacturer, Roche, has made the revisions to clarify the potential risk associated with concomitant use of the medication with calcium or

calcium-containing solutions or products. The Rocephin full prescribing information was updated in May 2007 to add new information about the interaction

between ceftriaxone and calcium-containing products on the basis of the postmarketing reports in neonates, which involve the potential risk of life-threatening and fatal results. Although no cases of ceftriaxone-calcium precipitates

have been reported in patients other than neonates, the potential for this interaction exists in patients of any age.

As a result of these observations, the FDA recommends that ceftriaxone not be mixed with calcium-containing products and not administered in the same or different infusion lines or sites in any patient within 48 hours of each other.

For more information follow the link

<http://www.fda.gov/Medwatch/SAFETY/2007/safety07.htm#Rocephin>