

The Prescription

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Rosiglitazone Safety Concerns

Editor: Brandi Kelly, PharmD

Dear Healthcare Provider,

We have been asked by University Health System to provide guidance to healthcare providers regarding the use of pioglitazone (Actos®) for patients with diabetes. Pioglitazone and rosiglitazone (Avandia®) are insulin-sensitizers of the thiazolidinedione (TZD) class. Only Actos® is available on the University Health System formulary. First, some background...

On May 21, 2007 the June 14th issue of the *New England Journal of Medicine* was made available online. In this issue, Nissen and Wolski published a meta-analysis which suggested a significant increase in the risk of myocardial infarction associated with rosiglitazone (Avandia®) treatment and an increase of similar magnitude, albeit nonsignificant, in the risk of death from cardiovascular causes. This publication created a furor in the press and has resulted in a quandary for physicians and their patients. In our opinion, the scientific merit of this meta-analysis is limited due to at least 14 major weaknesses of the "study".

On June 5th, 2007 the July 5th issue of the *New England Journal of Medicine* was made available online. In this issue Home and colleagues reported an unscheduled interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study — a multicenter, drug-company sponsored, open-label, non-inferiority trial.

Whereas the 42 trials included in the published meta-analysis by Nissen and Wolski generally were directed at the treatment of hyperglycemia and were not designed or powered to study potential adverse events such as cardiovascular disease, the RECORD trial was specifically designed to examine the effect of

rosiglitazone (in combination with oral agents and insulin) on cardiovascular outcomes. While the results of the interim analysis are underpowered to give a conclusive answer, the results show a very small, statistically insignificant increase in cardiovascular outcomes in the rosiglitazone treated patients. Considering the low power of the study, the use of multiple oral agents plus insulin in the rosiglitazone treated diabetic patients and the slight increased risk for cardiovascular events reported in the interim analysis, it is highly unlikely that the study ever will establish a cardiovascular benefit for rosiglitazone.

Unlike rosiglitazone, pioglitazone (ACTOS) has been studied in a prospective, randomized trial of cardiovascular outcomes, called Prospective PioglitAzone Clinical Trial In Macrovascular EVEnts (PROACTIVE).¹ The primary end point of PROACTIVE was a broad composite that included coronary/peripheral vascular events – demonstrated a trend toward benefit from pioglitazone (hazard ratio = 0.90; P=0.095).

The second principal end point, consisting of myocardial infarction, stroke, and death from any cause, was significantly improved in the pioglitazone treated patients (hazard ratio = 0.84; P=0.027). We agree with Dr. Nissen's conclusion about pioglitazone that this thiazolidinedione has been shown in a large, prospective double-blind study to reduce the risk of cardiovascular events in diabetic patients with a previous cardiovascular event.

Although pioglitazone and rosiglitazone belong to the insulin sensitizing thiazolidinedione class of antidiabetic drugs, there are significant differences between the two TZDs with respect to the genes which they turn on and off. From the clinical standpoint, one major difference relates to the effect of the two thiazolidinediones on the plasma lipid

profile. Both a meta-analysis (*Arch Int Med* 164:2097-2104, 2004) and a head-to-head comparison (*Diabetes Care* 28:1547-1554, 2005) have demonstrated that rosiglitazone tends to cause an increase in the plasma LDL cholesterol and triglyceride levels, whereas pioglitazone significantly reduces the plasma triglyceride concentration and has no significant effect on LDL cholesterol concentration while decreasing the number of LDL particles (apo B100).^{2,3} Although both TZDs raise the plasma HDL cholesterol concentration, pioglitazone

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is twice as effective as rosiglitazone in increasing HDL levels. These differences in plasma lipids may explain, in part, the observed reduction in cardiovascular risk in pioglitazone treated diabetic patients (PROACTIVE), and the failure to observe any decrease in cardiovascular events in diabetic patients treated with rosiglitazone.

As part of a separate issue (i.e., distinct from cardiovascular events), the FDA in April of 2007 determined that both rosiglitazone and pioglitazone should have black box warnings placed in their package inserts to highlight the increased risk of congestive heart failure. TZDs stimulate sodium reabsorption by the kidney and the increase in fluid volume may result in congestive heart failure in patients with underlying cardiovascular dysfunction. This fluid retention is a class effect of the thiazolidinediones (TZDs). There is no evidence that the TZDs have any direct negative effect on cardiac function. Fluid retention (edema) and CHF have been recognized as side effects of the TZDs since their introduction to the U.S. market and both drugs have prominent warnings regarding the increased risk of congestive heart failure in the Warnings Section of their package inserts. Despite this, patients with Class III-IV congestive heart failure continue to be started on TZDs and the FDA felt a stronger warning was warranted.

It is important to note the decision to place a black box warning for congestive heart failure predated and is unrelated to the *NEJM* articles about the possible increased risk of cardiovascular events with rosiglitazone.

What do we recommend for our patients on Actos®? First, patients on Actos® can be reassured that Actos is not associated with an increased risk of cardiovascular events. The recent *NEJM* study suggesting an increase in cardiovascular events is limited to Avandia® and is poorly substantiated by the data presented in the article. Second, you should be aware of the increased risk of congestive heart failure in patients given Actos®. Patients who develop edema should be monitored closely for signs and

symptoms of CHF, and excess fluid retention should be treated with a diuretic.

Sincerely,
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Note: The FDA advisory panel held a meeting on July 30th, several weeks after this letter was composed. The panel voted on two statements. They voted overwhelmingly that the evidence supports an increased risk of cardiovascular events with Avandia® use. They also voted overwhelmingly that Avandia® should remain on the market. While the FDA is not required to follow the panel's recommendations, they frequently do. More of the latest information regarding this issue is available through the FDA website at <http://www.fda.gov>.

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Correction: In the Spring 2007 edition of *The Prescription*, sitagliptan (Januvia™) was erroneously recorded as an intranasal glucocorticoid. Please note that sitagliptan was approved for use by the FDA in October of 2006 and is categorized as a dipeptidyl peptidase IV (DPP-IV) inhibitor used in the treatment of diabetes. Sitagliptin slows the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). The incretin hormones are released continuously throughout the day and are released in increased levels in response to meals. Their role is to increase insulin synthesis and release from the pancreas in response to meals. GLP-1 decreases glucagon secretion from the pancreas leading to decreased hepatic glucose production. Additionally, GLP-1 slows gastric emptying time leading to a lower peak in the glucose level.

Serotonin Syndrome

By Becky Brady, Pharm.D., UHS General Practice Resident Intern

The 2004 Report from the Toxic Exposure Surveillance System, an annual evaluation system for 62 poison control centers in the US, reported 299 deaths from antidepressants. Of these, 103 were from the use of selective serotonin reuptake inhibitors (SSRIs).¹ As antidepressant use increases among the population, special attention must be paid to drug interactions that can cause dangerously elevated serotonin levels leading to Serotonin Syndrome. Serotonin Syndrome is composed of a group of symptoms resulting from abnormally high levels of serotonin in the central nervous system. These symptoms are not always present and can range from insignificant to life threatening, leading to variability in clinical findings and difficulty in diagnosis.² Serotonin Syndrome frequently occurs because of drug-drug interactions between common inpatient and outpatient medications, and requires continued review of the patient's medication history. The existing treatment options have not been well studied. Therefore, supportive care and prevention of the syndrome continue to be the mainstays of therapy.³

Serotonin is a tightly regulated hormone that affects many areas of the brain and periphery. Its synthesis occurs after L-tryptophan hydroxylation or decarboxylation, and then it is stored in presynaptic vesicles until axonal stimuli cause serotonin release into the presynaptic space. Like other hormones, serotonin exerts its actions by binding to receptors that in turn cause certain actions. Seven known serotonin receptors exist in the brain called 5-hydroxytryptamine (5-HT) receptors, and they are further divided into members in each family. In addition, there also are serotonin receptors in the periphery. Each receptor is located in a different area of the brain or periphery, leading to different actions upon stimulation. For example, central nervous actions of serotonin depend on which receptor is stimulated and include influence on wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, sexual behavior, nociception, and motor tone. In the periphery, serotonin affects vascular tone and gastromotility.³ The amount of receptor stimulation is dependent on the level of serotonin available to the receptors, and therefore it is important to understand what affects serotonin levels.

The level of serotonin is determined by a number of mechanisms including reuptake actions, feedback loops, and metabolizing enzymes. Once serotonin is released into the presynaptic space, it binds to and stimulates post synaptic receptors. After receptor stimulation, it binds to presynaptic receptors in a feedback loop to inhibit further release of serotonin. Then it is incorporated back into the presynaptic vesicle and metabolized by monoamine oxidase subtype A (MAO).³

Drug design affecting serotonin levels has therefore resembled each of these regulatory mechanisms as well as targeted specific serotonin receptors in an effort to evoke specific actions.

Many medications affect serotonin levels by acting on the mechanisms surrounding serotonin regulation. For example, SSRIs such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram are used to treat depression. The antidepressive actions occur because the reuptake mechanism of serotonin is inhibited and serotonin levels increase leading to more serotonin receptor stimulation. The monoamine oxidase inhibitors (MAOIs) such as moclobemide, clorgiline, phenelzine, and isocarboxazide also have antidepressant effects by preventing the degradation of serotonin leading to increased amounts in the storage vesicles. The class of medications called the triptans including sumatriptan, rizatriptan, naratriptan, eletriptan, and frovatriptan, mimic serotonin's stimulation of the 5-HT receptors in the treatment of migraines.³

Serotonin Syndrome develops when abnormally high levels of serotonin stimulate serotonin receptors causing an exaggerated physiologic response. Therefore, the symptoms of serotonin syndrome are extreme reactions to the normal processes which serotonin regulates. Patients can present with varying degrees of autonomic, neuromuscular, and mental status changes. Autonomic changes include diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, or diarrhea.

Neuromuscular changes include tremors, muscle rigidity, myoclonus, or hyperreflexia. Mental status changes include anxiety, agitated delirium, restlessness, and disorientation.^{2,3} Elevated serotonin levels occur either from an overdose of one or the concomitant use of more than one serotonergic agent.⁴

Identifying medications that can elevate serotonin levels is an important intervention in preventing Serotonin Syndrome. Common interactions include too high of a dose for an antidepressant, more than one antidepressant, or the concomitant use of antidepressants with other less commonly known serotonergic agents.

Some of these agents were mentioned above, such as the triptans used for the treatment of migraines. Another serotonergic agent is linezolid, a new antibiotic, which has MAOI properties and can elevate serotonin levels.⁵

Outside of serotonergic agents, it is also important to watch for agents that affect the metabolism of serotonergic agents. For example, clarithromycin, a common macrolide antibiotic and CYP 3A4 inhibitor, can elevate levels of SSRIs that undergo metabolism by this enzyme. Two common SSRIs that undergo CYP 3A4 metabolism and have been implicated in Serotonin

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Syndrome are paroxetine and fluoxetine.⁶

Treatment of Serotonin Syndrome involves discontinuation of the offending agents, supportive care, and possible sedation and/or administration of serotonin antagonists. The level of care depends on the severity of the case. Mild cases are most often treated with supportive care and benzodiazepines such as diazepam, although diazepam has been found to be effective in rat studies, and has not been studied in humans. Serotonin antagonists such as the 5-HT_{2A} antagonist cyproheptadine can be used if benzodiazepines fail to control agitation. Other symptoms which may require treatment include autonomic instability and hyperthermia. Autonomic changes including hypertension and tachycardia can be treated with short-acting agents such as esmolol and nitroprusside. Hypotension can be treated with low doses of direct-acting sympathomimetic amines. Hyperthermia is caused by muscle activity and therefore should not be treated with anti-pyretics. Temperatures above 41°C should be treated by inducing sedation using vecuronium and intubation.^{2,3}

Prevention is key. Medication review not only of current medications but medications that have recently been discontinued is very important. Proper physician education, prescribing practices, and continual medication review are effective ways of preventing Serotonin Syndrome from developing.³

Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.
Drugs associated with the serotonin syndrome
Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolid (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, <i>Hypericum perforatum</i> (St. John's wort), Panax ginseng (ginseng)
Other: lithium
Drug interactions associated with severe serotonin syndrome
Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anaf-ranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolid and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

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ACE Inhibitors in the First Trimester of Pregnancy

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A recent study in the *New England Journal of Medicine* retrospectively assessed data from the Tennessee Medicaid database and reported malformations in 7.12% of infants exposed to an angiotensin converting enzyme inhibitors (ACE inhibitors) during the first trimester of pregnancy. Infants exposed to other antihypertensive medications and the control group had much lower rates of malformations (1.73% and 2.63%, respectively).

A total of 29,507 infants from the Tennessee database were included for analysis. Two-hundred and nine infants were exposed to ACE inhibitors during the first trimester and 202 infants were exposed to other antihypertensive medications. Infants born to mothers with diabetes or mothers who took ACE inhibitors, angiotensin receptor blockers (ARBs) or antihypertensive medications after the first trimester were excluded.¹

Previously, use of ACE inhibitors during the first trimester of pregnancy was believed to be relatively safe. However, the data was limited. A survey of 18 Michigan Medicaid recipients from 1985 to 1992 showed no association between ACE inhibitor exposure during the first trimester of pregnancy and congenital birth defects. Data regarding the harmful effects of ACE inhibitor use during the second and third trimesters of pregnancy has been well established for years.² Currently, the FDA labels ACE inhibitors as pregnancy category C during the first trimester of pregnancy and pregnancy category D during the second and third trimesters.³

The renin-angiotensin system plays a major role in fluid volume

and blood pressure homeostasis. Activation of angiotensin II causes fluid retention and vasoconstriction, leading to an increase in blood pressure. ACE Inhibitors and ARBs inhibit production or activity of angiotensin II, thereby decreasing blood pressure. During fetal development, angiotensin II contributes to many processes, which are important to consider when deciding which antihypertensive medication to use to treat hypertension in pregnancy.⁵

One role of angiotensin II during fetal development is to maintain adequate glomerular filtration in the kidneys because the fetal kidney is a low perfusion pressure system. Also, the main source of amniotic fluid is from fetal urine. When a mother takes an ACE inhibitor, the activity of angiotensin II in the kidneys is blocked leading to poor perfusion to the kidneys and decreased fetal urine output. In turn, the infant develops oligohydramnios, which is a decrease in amniotic fluid levels. Complications of oligohydramnios include hypoplastic lungs, limb contractures, respiratory failure and death. ACE inhibitor exposure is also associated with incomplete formation of the calvarial bones in the skull, resulting in enlarged sutures and fontanelles. While brain development has not been shown to be affected, the enlarged fontanelles and sutures leave the brain unprotected.⁵

Increased risk of major congenital malformations due to ACE inhibitor exposure during the first trimester of pregnancy must be considered and discussed with women of child-bearing age who

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Table 1
Rates of Malformations (% patients)¹

Malformation	ACE Inhibitor (N=209)	Other Antihypertensive Medication (N=202)	No Antihypertensive Medication (N=29,096)
Total	7.12	1.73	2.63
Cardiovascular	2.90	0.70	0.78
CNS	1.46	0	0.33
Other	2.71	0.95	1.55

ACE Inhibitors in the First Trimester of Pregnancy

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may be candidates for therapy with ACE inhibitors. Prior to a planned pregnancy, the patient's regimen should be changed to an antihypertensive medication that has not been believed to be harmful when taken during pregnancy. Alternative antihypertensive medications considered safe to use during pregnancy include methyldopa and beta blockers. In addition, women who have taken an ACE inhibitor during pregnancy should seek early prenatal care.⁶

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Table 2
FDA Pregnancy Category Labeling⁴

Category	Definition
A	Adequate, well controlled studies in pregnant women have not shown increased risk of fetal abnormalities
B	Animal studies show no evidence of harm to the fetus, but there are no adequate, well controlled studies in pregnant women OR Animal studies show fetal risk but adequate, well controlled studies in pregnant women show no risk to the fetus
C	Animal studies show increased risk to the fetus, but there are no adequate, well controlled studies in pregnant women OR No animal studies and no adequate, well controlled studies in pregnant women
D	Adequate, well controlled or observational studies in pregnant women show risk to fetus, but the benefit of therapy may outweigh the potential risk
X	Adequate, well controlled or observational studies in pregnant women or animals show fetal abnormalities and the use is contraindicated in women who are or may become pregnant