



Thiazolidinediones and Heart Failure

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Thiazolidinediones (TZDs) like rosiglitazone (Avandia™) and pioglitazone (Actos™) have become increasingly popular drugs in the treatment of type 2 diabetes. These agents work by binding and activating a protein called PPAR γ , although the exact target tissues and the mechanisms by which they work are still poorly defined. TZDs have a variety of side effects, such as weight gain and occasional muscle soreness, although in general they are extremely well-tolerated. Another rare but possible side effect is fluid retention, which can worsen congestive heart failure and could be associated with pulmonary edema, but not much is known about how this occurs or even how often it occurs. A series of small but interesting studies now takes a closer look at this phenomenon, and a small red flag of concern has been raised about using these drugs in patients who may already have borderline heart function.

Two new retrospective studies have looked at this issue. In the first, physicians at the University of Texas looked at the cases of six men who developed significant heart failure while taking TZDs for type 2 diabetes. In all of the cases there were other predisposing factors for heart failure, including ischemic heart disease or kidney failure, and in 5 out of 6 cases, patients were taking maximal doses of TZD. The cases represented less than 1% of all TZD patients over the 9 month study period at their hospital, and all the cases resolved after TZDs were discontinued. Interestingly, traditional treatments for heart failure, like diuretics, were not particularly effective until the TZD was stopped, further implicating the drug as a cause of the problem. In the second study, a group used insurance records to identify TZDs as a risk factor for heart failure; overall, TZDs increased the risk of heart failure by a factor of 1.7.

How do TZDs cause this problem? Well, no one is totally sure, but the smart money appears to be on their ability to increase intravascular volume. TZDs increase blood volume by 6-7%, enough to cause blood cell dilution that can lead to anemia in some cases. There may also be an effect of TZDs to increase the amount of fluid that leaks out of blood vessels and into susceptible tissues, such as the lung, kidney, and lower extremities. It is unlikely that TZDs adversely affect the heart itself, as studies have shown, if anything, a positive effect on cardiac contractility in the presence of these agents.

A few things are important to understand before tossing out your TZDs. First, people with diabetes are more prone to heart failure than non-diabetics. The exact rate is a bit difficult to calculate, because different folks use different definitions of heart failure and measure it in different ways. Nonetheless, as many as 12% of people with type 2 diabetes are estimated to have some degree of heart failure, although many may not even be aware of it. Diabetes increases the risk of heart failure in several different ways, in part by increasing the likelihood of atherosclerosis (which itself leads to heart failure) in addition to direct effects of high glucose on heart muscle. So TZDs may add only a very small increment to the total number of diabetics with heart failure.

Another thing that's important to know is that there are limited treatment options for patients with both diabetes and heart failure. The most popular oral agent, metformin, is contraindicated in heart failure, and even though recent studies show that lots of doctors and patients are ignoring this issue, it seems prudent at present to avoid this situation.

Sulfonylureas are not specifically contraindicated, but many doctors prefer not to use them when there is likely to be variable absorption and excretion, as occurs commonly in heart failure. Insulin is the drug of choice, even though peripheral edema from severe heart failure can adversely affect its absorption from the skin, and can also impair excretion from the kidney. So in diabetes and heart failure, it can be 'damned if you do, and damned if you don't'.

Third, TZDs have been shown to have a variety of other, beneficial effects on the cardiovascular system. As mentioned earlier, they may increase the ability of the heart to contract, and they definitely reduce blood pressure, albeit to a modest degree. They have also been shown to have a series of profound effects on changing the balance of cholesterol trafficking in the vessel wall so as to reduce atherosclerosis. These benefits have not been quantified in human populations yet, so it's difficult to know if they outweigh the risks of heart failure in type 2 diabetics.

Despite these caveats, the American Heart Association and American Diabetes Association have just released a joint manifesto that cautions about the use of TZDs in cases of known or suspected heart failure. These recommendations include avoiding TZDs in patients with moderate or severe heart failure. Those with mild heart failure can still use TZDs, but are advised to start with very low doses that can be increased slowly and cautiously. Patients are advised to report significant weight gain (more than 6-7 lbs), swelling of legs or feet, or the sudden onset of shortness of breath.

These are sensible recommendations, and should be followed for the time being. Time (and more research!) will ultimately tell whether TZDs have a net positive or negative effect on the heart. We would also benefit from better tools that would allow us to reliably pinpoint who is at greatest risk from these medications, and who should not be denied their positive effects.

To read Dr Rosen's bio click here

<http://www.diabetesincontrol.com/rosen/bios.shtml>

Reference:

Diabetes Care 26: 2983 (2003)

Mayo Clinic Proceedings 78: 1088 (2003)

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