Characterization of Edema Associated with Pioglitazone by Measurement of Plasma Volume

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A. Study Purpose and Rationale

Worldwide, there are about 143 million patients with diabetes mellitus type 2, almost 5 times more than estimated 10 years ago.[1] The underlying pathophysiology of type 2 diabetes is based on insulin resistance and beta cell dysfunction. Other abnormalities also include dyslipidemia with elevated triglycerides and low HDL. CHF is prevalent in 11.8% of diabetic subjects. Both diastolic and systolic dysfunction are increased in diabetics compared to nondiabetics. Diabetes, in turn, is the largest comorbidity of patients with heart failure and diabetes also adversely affects outcomes of cardiovascular disease.[2]

The thiazolidinediones including pioglitazone, rosiglitazone, and troglitazone (the latter no longer available due to cases of severe hepatic toxicity) are a class of agents used in the management of type 2 diabetes that can lower fasting glucose and hgb A1C. These agents affect glucose metabolism by improving insulin sensitivity, thus more effectively addressing underlying metabolic defect of type 2 diabetes. In addition, the thiazolidinediones have added benefits of increasing HDL and lowering triglyceride levels, as well as lower diastolic blood pressure. Although these agents can cause weight gain, there is redistribution away from visceral adiposity to subcutaneous fat which is associated with reduced cardiovascular risk.

The thiazolidinediones' mechanism of action is through it actions as high affinity ligands for PPARγ, or peroxisome proliferator- activated receptor gamma. PPARγ is a transcription factor belonging to the nuclear receptor superfamily. PPARγ is highly expressed in adipose tissue, where it plays a major regulatory role in adipocyte differentiation and the expression of adipocyte specific genes involved in lipid metabolism.

More than glycemic control, there may be possible wider utility of thiazolidinediones in various clinical conditions such as HIV lipodystrophy, lipid disorders, impaired glucose tolerance, and cardiac diseases such as coronary artery disease and heart failure, systolic and diastolic. One study suggested that PPARγ might play a critical role in the inhibition of cardiac hypertrophy in vitro and in vivo when they examined effects of thiazolidinediones on angiotensin II induced hypertrophy in neonatal rat cardiac myocytes and on pressure-overload-induced cardiac hypertrophy in mice.[3] The investigators found the thiazolidinediones inhibited AII-induced upregulation of skeletal alpha-actin and atrial natriuretic peptide genes as well as inhibited increase in myocardial cell surface area. In their study, treatment of mice with pioglitazone inhibited pressure overload-induced increases in heart weight-to-body weight ration, wall thickness, and myocyte diameter.

Thiazolidinediones may also have anti-inflammatory effects. Activation of PPAR gamma inhibits cardiac expression of TNF-alpha, interleukin-1B and –6, inducible nitric oxide synthase, scavenger receptor A in monocytes and monocyte-derived macrophages. PPAR gamma also inhibits growth factor-induced proliferation and migration of vascular smooth muscle cells. Therefore, these effects on macrophages, vascular smooth muscle cells and vascular endothelial cells are thought to be beneficial in preventing atherosclerosis and the inhibition of TNF- alpha may be beneficial in preventing the development of heart failure.

However, there are many concerns raised regarding side effects of the thiazolidinediones. Edema is the most common side effect, occurring in up to 11% of patients and up to 15% of patients on concurrent insulin therapy, however this edema is uncharacterized and its mechanism is unknown. Heart failure is another concern. In a study presented at 2002 American College of Cardiology Annual Scientific Session in March, 2002, a retrospective study looking at insurance claim forms of 8,000 type 2

diabetics treated with troglitazone, rosiglitazone, or pioglitazone and 41,000 not on a glitazone showed an increased risk of developing heart failure in the glitazone group (2.6% vs. 4.5%) after a follow-up period of 9 months. However, in a study performed at our institution examining myocardial chamber properties in severe systolic heart failure during treatment with pioglitazone, 7 subjects, age 60± years with systolic failure EF 22±3 on standard therapy for heart failure underwent 3-D echocardiography before and after therapy with pioglitazone. The results of the study showed no difference in LV volumes, mass, EF, Ees, Ea, Ea/Ees ratio from baseline after therapy.[4] In another study, a multi-center 48-week trial, 154 NIDDM pts were randomized to receive troglitazone or glyburide. 2-D echo and pulsed doppler were used to measure LV mass index, cardiac index, and stroke volume index. Results showed no statistically significant increase in LVMI. There were statistically sig. increases in CI and SVI as well as statistically sig. decrease in diastolic pressure in the troglitazone-treated group.[5]

Understanding the mechanism of edema related to thiazolidinediones would help to distinguish edema from clinical heart failure. Also it would provide insight into ways of overcoming the edema associated with this class of agents. A review of literature shows that the thiazolidinediones may cause edema through several possible mechanisms. First, both the glitazones and calcium channel blocking drugs inhibit the slow L-type calcium channel in cardiac and vascular smooth muscle.[6] In vascular smooth muscle, these drugs decrease arteriolar resistance as a result of vasodilatation with a resultant decrease in blood pressure. Peripheral edema is an adverse event seen during treatment with calcium channel blockers as well as with the glitazones. The peripheral edema from calcium channel blockers is related to redistribution of fluid from the vascular space into the interstitium. In one study of 12 healthy subjects, for example, a single dose of nifedipine increased the foot volume despite also increasing sodium excretion. Thus, treatment of this form of edema with a diuretic may not relieve the edema. On the other hand, edema is much less common when a dihydropyridine is given with an angiotensin converting enzyme inhibitor. This effect is probably related to venodilation by the ACE inhibitor which helps remove the fluid sequestered in the capillary bed by the arteriolar dilation from the calcium channel blocker.

Another possible mechanism by which TZD's may cause edema is through VEGF. Troglitazone and pioglitazone increased VEGF secretion in a time and dose dependent manner and also increased levels of VEGF mRNA.[7] In another study, when Japanese patients were screened for plasma VEGF, they found levels to be significantly increased in troglitazone treated subjects.[8] If the thiazolidinediones caused edema via either calcium channel inhibition or stimulation of VEGF production then they would cause decrease in plasma volume.

However, there is also evidence arguing for the TZD's causing increased plasma volume. In preclinical studies done by Takeda, pioglitazone caused increased plasma volume in animals.[9] Also, there has been the observation that pioglitazone can cause mild decreases in hemoglobin levels in patients, which may be related to increased plasma volume.

Questions and Study Aims:

1. To determine characteristics of edema associated with thiazolidinediones: Is it increase in plasma volume or interstitial edema?
2. Secondary question: Does pioglitazone cause changes in the myocardium?

B. Study Design and Statistical Analysis

The study design proposed is a prospective randomized, double-blinded, placebo-controlled interventional study.

The following baseline tests will be obtained from all study subjects: vital signs, physical exam, weight, height, HgbA1C, fasting glucose, C7, lipid profile, UA, microalbumin, plasma volume and total blood volume measurements, 2-D transthoracic echo (EF) with tissue doppler of myocardium (to assess for diastolic dysfunction), 3-D echo (to measure cardiac mass, volume, contractility, stroke volume).

Both groups will receive counseling about nutrition and exercise, as well as continuation of oral hypoglycemic agents or insulin. In addition, patients in the treatment arm will receive pioglitazone 30mg

po QD while the patients in the control group will receive placebo or non-thiazolidinedione oral hypoglycemic agent if the patient is a newly-diagnosed diabetic who has not yet been prescribed diabetic treatment.

Randomization will be performed by computer-generated randomization through the Irving Center research pharmacy. Placebo /(or other oral hypoglycemic agent if the patient is not already treatment for diabetes) will be prepared by the research pharmacy in identical form and color to pioglitazone, the study drug.

Total follow-up period will be 48 weeks. Regular follow-up with physical exam, weight and repeat CBC, C7, LFT's, and fasting glucose will be done every 4 weeks. Plasma volume assessments, 2-D and 3-D echocardiography are to be performed at weeks 0, 16 and 48. Dietary counseling will be provided to both treatment and placebo groups.Proposed method of statistical analysis to be used is the unpaired t-test. Sample size is derived using the equation:

n(in each arm)=1+16(std devn/effect)^2 Using a mean plasma volume 2670cc$\pm$SD of 106cc and estimated effect size of 140cc est. by 2L* x 0.07=140cc, and using the above sample size calculation for power of 80% and testing at p=0.05, number of subjects in each arm required is 11 patients. Analysis will be based on the intention-to-treat principle.

C. Study Procedure

Measurement of plasma volume will be based on the indicator-dilution principle:

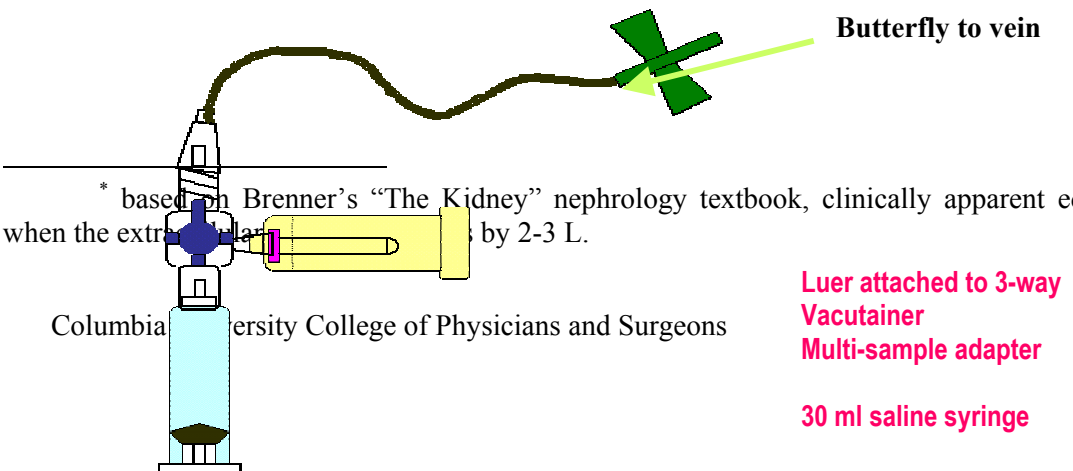
1. Consider an unknown volume of fluid = V,

2. Into which is put a known exact quantity – Q – of an indicator,

3. After thorough mixing of the indicator in the compartment, a small measured amount of fluid is removed, and the concentration of the indicator in it is measured = c ,

From this it can be calculated that **V = Q/C**

Plasma volume can be measured by using radioactive iodine(I^{131})attached to albumin. Since plasma albumin do not leak readily out of the plasma compartment of the blood, neither will the dye or (I^{131}). The Daxor BVA-100, a semi-automated blood volume analyser, in conjunction with a single use diagnostic kit will be used to measure plasma volume. The Max-100 is a US. Patented quantitative injection syringe. It is a 1mL polycarbonate syringe designed to be used as a unit dose, isotope carrying assembly. The syringe comes pre-filled with 1mL of saline containing 10-25 microcuries of I^{131}in the form of HAS-I^{131} . Blood samples are taken at approximately 0, 12, 18, 24, and 36 minutes, separated, placed into counting tube, and together with standard background and control samples placed in the BVA-100. Technical analysis consists of an evaluation of five separate blood volume collection points with mathematical evaluation of consistency. Technical evaluation is reported as acceptable or unacceptable.



* based on Brenner's "The Kidney" nephrology textbook, clinically apparent edema develops when the extracellular [illegible] by 2-3 L.

D. Study Drugs

Pioglitazone 30mg po qd is FDA approved for use in improving glycemic contro in patients with type 2 diabetes and is indicated for monotherapy as well as use in combination with a sulfonylurea, metformin, or insulin.

E. Medical Device

N/A

F. Study Questionnaires

Questionnaires will be used to assess patients' eligibility for the study as well as during follow-up to assess symptoms associated with treatment.

G. Study Subjects

Subjects to be screened will be adults 18 years or older.

Inclusion criteria: Type 2 diabetics without clinical heart failure previously not on a thiazolidinedione.

Exclusion criteria: NYHA class II-IV heart failure, nephrotic syndrome, renal disease, liver disease, edema, echocardiographic evidence of systolic heart failure, diuretic use, calcium channel blocker use, or pregnancy.

H. Recruitment of Subjects

Recruitment of potential subjects will be through primary physicians and posted flyers in the Columbia-Presbyterian Medical Center.

I. Confidentiality of Study Data

All study data will be coded with an unique code number for each study subject. Data will be stored in a secure location, accessible only to the investigators.

J. Potential Conflict of Interest

None

K. Location of the Study

CPMC clinical care areas including the Irving Center for Clinical Research, and department of internal medicine

L. Potential Risks

Potential risks include possible side effects of pioglitazone such as edema, hypoglycemia, anemia, or liver enzyme abnormalities. Subjects will have routine monitoring of their hepatic function tests, CBC, C7, and glucose levels.

M. Potential Benefits

Potential benefits include potential benefits from pioglitazone therapy as described in background section.

N. Alternative Therapies

Alternative therapies include other oral hypoglycemic agents such as metformin and sulfonylureas, as well as insulin

O. Compensation to Subjects

No financial compensation will be offered

P. Costs to Subjects

Costs that subjects may incur include costs of transportation to the medical center

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

In comparing relative radiation exposures, the exposure risk of a plasma volume determination is less than a single routine chest X-ray. The radiation dosage of a plasma volume determination is 10-25 microcuries compared to 50 microcuries from single CXR. In some cases, where required, a dosage as low as 1-2 μcuries may be used for a blood volume determination (the test will require more time).

S. References:

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