NEW PLAYERS IN STROKE: PIOGLITAZONE

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Prevention of further vascular events for stroke survivors, and those after transient ischemic attack, is of major importance as recurrent strokes and myocardial infarctions are major sources of morbidity and mortality.

Current strategies for preventing such vascular events include antithrombotic therapy, hypertension control, lipid management, and carotid revascularization yet despite these effective strategies many patients still experience recurrent events and new therapeutic approaches are therefore needed.

Insulin resistance is a common and important risk factor for vascular disease. It affects almost all patients with type 2 diabetes and 50% of non-diabetic patients with ischemic stroke or TIA. Insulin resistance results from defective intracellular signaling that affects glucose transport and cellular metabolism. The physiological consequences include metabolic and cellular events that promote atherosclerosis. In epidemiologic research, insulin resistance has been associated with several vascular risk factors including endothelial dysfunction, vascular inflammation, dyslipidemia, hypertension, and abnormal fibrinolysis.

Insulin resistance, abdominal obesity, hypertension, low HDL cholesterol, hypertriglyceridemia, and ischemic vascular disease occur together in individuals more often than can be explained by chance. Originally it was called the insulin resistance syndrome and now it is termed the metabolic syndrome. This syndrome is associated with increased risk for cardiovascular disease, all-cause mortality and stroke.

Based on available data, insulin resistance was found to be an independent risk factor for stroke; adjusted relative risk for ischemic stroke appears to be 1.5-3.4.

Drug therapy for insulin resistance includes thiazolidinediones (TZDs) which activate a novel subclass of nuclear receptor, the peroxisome proliferator activated receptor gamma (PPAR-γ). TZDs are potent inhibitors of vascular inflammation, and this may be a key mechanism for their vasoprotective effect. The net effect of TZDs on vasculature is to prevent atherosclerosis.

Pioglitazone is a commonly used TZD. It reduces insulin resistance and its therapeutic potential has been demonstrated in research showing that it has profound effects on numerous biological events related to the insulin resistant state, including inflammation, vascular cell proliferation, dyslipidemia, vascular lesion formation, and thrombosis.

The PROactive study was the first clinical trial to test the effectiveness of pioglitazone for prevention of cardiovascular disease in diabetic patients. The primary endpoint was reduced by 10% and the secondary endpoint (heart attacks, stroke and death) by 16% with pioglitazone. Subgroup analysis for the 984 patients who entered the study following a stroke revealed an almost 50% stroke risk reduction (5.6% on pioglitazone vs. 10.2% on placebo).

Based on these associations and data, it has been hypothesized that modification of insulin resistance may reduce the incidence of stroke and MI.

The aim of the Insulin Resistance Intervention after Stroke (IRIS) trial is to determine if pioglitazone is effective in lowering the risk for stroke or myocardial infarction among non-diabetic men and women with a recent ischemic stroke or transient ischemic attack (TIA) and insulin resistance. IRIS is a randomized, double-blind, placebo controlled trial that will enroll 3136 participants and all patients will be followed for a minimum of 3 years. IRIS has 90% power to detect a 20% reduction in risk for the primary endpoints of fatal and nonfatal stroke and myocardial infarction.

The IRIS trial will determine the effectiveness of this new strategy and since insulin resistance is estimated to affect 50% of stroke and TIA patients, this innovative treatment has the potential to benefit a large number of patients.