

Glycaemic and nonglycaemic effects of pioglitazone in triple oral therapy of patients with type 2 diabetes

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Theoretical premises

The most common treatment strategy of type 2 diabetes mellitus is to start with metformin and add sulphonylurea (or vice versa) and when this combination therapy fails, to add or replace it with insulin. An alternative is to add a thiazolidinedione (TZD).

TZD are selective ligands of the nuclear transcription factor peroxisome proliferator-activated receptors (PPAR γ), which improve glucose tolerance and decrease insulin resistance in patients with type 2 diabetes. They have positive effects on endothelial function, atherogenesis, fibrinolysis and immune function. TZD treatment has been associated with fluid retention, weight gain and peripheral oedema.

Purpose

To evaluate the efficacy of adding pioglitazone to treatment with metformin and insulin secretagogues in patients with type 2 diabetes mellitus and inadequate glycaemic control as well as the safety regarding the possible fluid retention with this therapy.

Efficacy was defined as percentage of patients achieving treatment goals of HbA1c <6.5%. Serum adiponectin levels were used as a measure of insulin sensitivity. Pro-insulin concentrations were measured to obtain insight into how therapy influenced β -cell function. NT-

pro BNP was measured as a cardiac marker, cystatin C to estimate glomerular filtration rate (GFR) and haemoglobin to assess a possible subclinical fluid retention.

Study design

Open-label prospective observational design including 66 patients with type 2 diabetes and secondary drug failure. Secondary drug failure was defined as HbA1c =6.5% (ref. 4-5.3%) at the two latest measurements with at least 8 weeks in between, during ongoing treatment with metformin (=1500 mg day) and glibenclamide (=7 mg day) or glipizide(=10 mg day) or glimepiride (=3 mg day) or repaglinide (=6 mg day) for at least 3 months. Other entry criteria were age between 30 and 75 years and body mass index (BMI) >20. 54 patients completed the study. The study had an with 26 weeks of follow-up with intermediate visits at 8 and 16 weeks.

The patients received a prescription of 30 mg pioglitazone daily in addition to their existing therapy with metformin and an insulin secretagogue. After 16 weeks the dose of pioglitazone was increased to 45 mg day if HbA1c was not <6.5% and the therapy was tolerated. At the end of the study one-third of patients were randomized to be followed with HbA1c measurements for another 3 months after withdrawal of pioglitazone (with the previous medication unchanged).

Results

HbA1c changes were greater in women ($P = 0.029$). After 26 weeks of treatment, HbA1c decreased from 7.8 ± 0.9 to 6.3 ± 0.9 ($P < 0.001$). In the 18 patients followed off-pioglitazone, HbA1c increased after 3 months from 6.1 ± 0.73 to 7.1 ± 0.9 ($P < 0.001$).

During the study there was a significant weight gain from 90 ± 15 to 94 ± 16 kg ($P < 0.001$) and an increase in BMI from 31 ± 4 to 32 ± 4 kg/m² ($P < 0.001$). Despite the increase in BMI there was a significant decrease in waist-to-hip ratio that was due to smaller increase in waist than hip circumference – supporting the view that TZDs promote redistribution of fat from abdominal to subcutaneous regions.

In addition, ALT decreased (reflecting a redistribution of fat from liver adipose depots), HDL cholesterol and triglycerides decreased but total cholesterol concentrations remained unchanged.

Adiponectin levels increased more than twofold and the increase correlated with the decrease in HbA1c ($P = 0.001$). There was also a highly significant decrease in proinsulin to insulin ratio ($P < 0.001$) without any significant changes in insulin levels. The highly significant decrease in the proinsulin to insulin ratio suggests an alleviation of the demands on β -cells and reduced β -cell stress.

NT-proBNP levels increased significantly after 26 weeks of treatment with pioglitazone.

Cystatin C increased from 0.96 ± 0.20 to 1.02

± 0.21 g L⁻¹ ($P = 0.004$) which corresponded to a $6.8 \pm 0.18\%$ change in GFR. The nature of this decrease is not known and needs further study. The individual change in GFR and NT-proBNP did not correlate with each other.

There was a significant decrease in haemoglobin concentrations ($P < 0.001$), probably through fluid retention.

The most common side effect was oedema reported by 10 patients (19%), in four (7%) of them transient. Twelve patients (22%) experienced mild hypoglycaemia, but the treatment was well tolerated and these types of side effects are frequently encountered with treatment with other glucose-lowering agents.

Limits

The open study design without a comparator limits; The most logical comparator after failure on two oral agents would be insulin, which is not easy to use in a double-blinded study.

Conclusion

The study indicates that pioglitazone is effective in reaching treatment goals in patients with secondary drug failure, but determines fluid retention, which in the majority of cases is mild and easily reversible. The treatment seems to also have additional positive effects on insulin sensitivity, β -cell stress, lipid profile and body fat distribution- with potential decrease of macrovascular complications.

Comment on the paper:

M. Dorkhan, M. Magnusson, A. Frid et al – Glycaemic and nonglycaemic effects of pioglitazone in triple oral therapy of patients with type 2 diabetes. *Journal of Internal Medicine* 2006; 260:125-133