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RESEARCH ARTICLE

Are all glitazones the same?†

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†This paper is based on a presentation given at the satellite symposium, 'Are all glitazones the same? Addressing insulin resistance as a fundamental issue', held at the 35th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Brussels, Belgium on 28 September 1999. This paper was updated relative to the issue of hepatotoxicity because of the US Food and Drugs Administration (FDA) analyses and the subsequent removal of troglitazone from the US market.

Abstract

This supplement focuses on the benefits of targeting insulin resistance through therapy with a new class of oral antidiabetic agents, the thiazolidinediones (TZDs) or 'glitazones'. There are important differences between the three TZD class members that warrant discussion to enable physicians to make rational and informed therapeutic choices between the agents. Overall the TZDs appear to be similar in their effects on blood glucose, as all class members have demonstrated effective glycaemic control, both as monotherapy and in combination with sulphonylureas, metformin or exogenous insulin. The safety profiles of the three agents are more diverse, with what appear to be 'TZD class effects', (probably mediated via activation of peroxisome proliferator-activated receptor γ [PPARγ]) and 'TZD-specific effects', which are unique to each agent and may be a consequence of differing chemical structures. While rosiglitazone and pioglitazone share some class effects with troglitazone, they have several characteristics that define them as unique agents. By tackling the control of type 2 diabetes through direct effects on insulin resistance, the TZDs represent an important new therapeutic tool for healthcare professionals.

Keywords insulin resistance; thiazolidinediones; type 2 diabetes; rosiglitazone; pioglitazone; troglitazone

Introduction

The symposium, 'Are all glitazones the same?', was held on 28 September 1999, on the occasion of the 35th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Brussels, Belgium. At the time of writing, the 1999 EASD meeting was the largest congress on diabetes ever to take place in the world, with more than 10 000 participants in attendance. The aim of our symposium and the proceedings published in this supplement to *Diabetes/Metabolism Research and Reviews* was to highlight the fundamental role of insulin resistance in type 2 diabetes, focusing on the benefits of targeting insulin resistance through therapy with a new class of oral antidiabetic agents, the thiazolidinediones (TZDs), or the 'glitazones' as they are otherwise known.

Management of type 2 diabetes – current status

In most cases, especially in overweight individuals, the major early pathological defect in type 2 diabetes appears to be the development of insulin resistance. Defective insulin secretion seems to be a phenomenon that occurs later in the course of the disease, largely explaining the progression towards insulin requirement [1]. As well as being a risk factor for the development of type 2 diabetes [2,3], insulin resistance is also associated with a constellation of metabolic disturbances, known as 'insulin resistance

syndrome', 'metabolic syndrome', or 'syndrome X' [4–6]. Early identifications in this clustering of metabolic disorders included hyperinsulinaemia, impaired glucose tolerance, hypertension, and dyslipidaemia [4]. More recently, several other markers have been recognised, including hyperuricaemia, high fibrinogen levels, and elevated plasminogen activator inhibitor-1 concentrations [5,6]. All these metabolic abnormalities have been shown to be strongly associated with abdominal (visceral) adiposity [7,8] and are considered to be risk factors for coronary heart disease [8]. This would suggest that individuals with insulin resistance syndrome may be prone to develop premature atherosclerotic disease [7–11]. Currently available oral antidiabetic agents do not effectively deal with the many metabolic disturbances associated with insulin resistance [12,13]. This is even true of the biguanide compound metformin – generally considered as the drug of first choice in patients with upper-body fat distribution [14] or obesity-related type 2 diabetes [15].

The UK Prospective Diabetes Study (UKPDS) showed that intensive glucose control with either sulphonylureas or basal insulin therapy maintained a lower HbA_{1c} by a mean of 0.9% over a median follow-up of 10 years, as compared with diet alone in newly diagnosed patients with type 2 diabetes [16]. This corresponded with a significant 25% reduction in the risk of diabetes-related microvascular complications [16]. However, data were less convincing for the effect of lowering blood glucose on macrovascular complications. The exception was found in a subgroup of obese patients who were receiving metformin therapy. Despite similar blood glucose control to that achieved by patients treated with sulphonylureas or insulin, the incidence of diabetes-related macrovascular complications was significantly reduced in this group [17]. These results, in addition to cardioprotective effects of controlling high blood pressure [18], indicate a clear need to consider factors beyond glycaemic control in the management of type 2 diabetes.

TZDs – new antidiabetic agents

Research is ongoing in the search for antidiabetic drugs that will allow physicians to better manage their patients. Recently, there has been particular interest in the central role of insulin resistance in the development of type 2 diabetes and associated risk factors for complications [13,19–21]. In this respect, the TZD family is an appealing new class of therapeutic agent for the treatment of diabetes, producing much enthusiasm among diabetologists and having been subject to extensive clinical research.

Following withdrawal of troglitazone from all markets, there are now two main members of the TZD class: rosiglitazone and pioglitazone (Figure 1) [22]. This class of agents represents a significant advancement in the treatment of type 2 diabetes. Through their innovative mechanism of action as agonists of the gamma isoform of

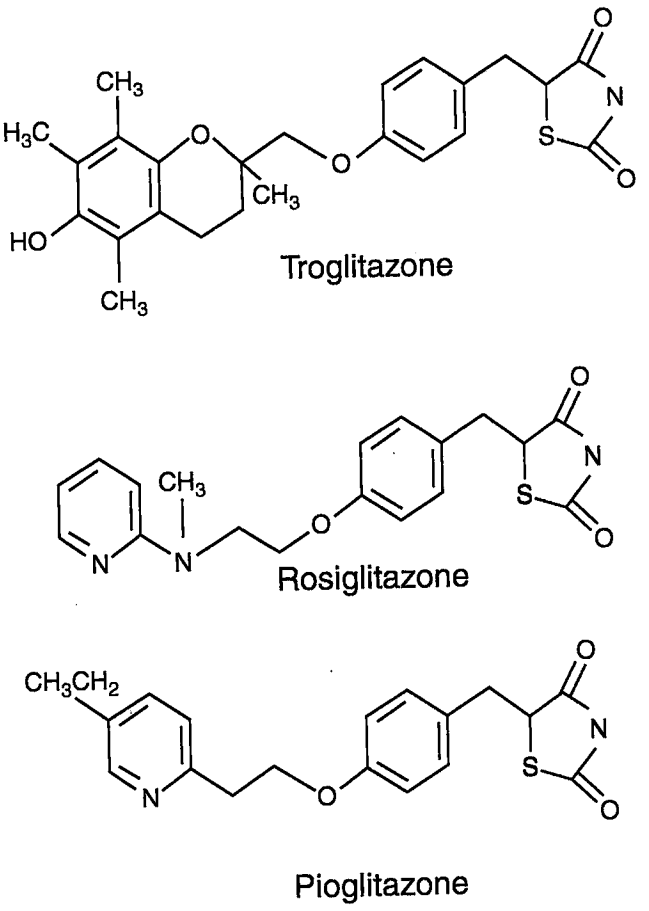

Figure 1. Chemical structures of troglitazone, rosiglitazone and pioglitazone

the peroxisome proliferator-activated receptor (PPARγ) [23], glycaemic control is improved by enhancing the sensitivity of skeletal muscle, adipose tissue and hepatocytes to circulating insulin. In addition to their effects on blood glucose regulation, TZDs also have the potential to favourably affect other risk factors associated with insulin resistance [13].

There are important differences between the three TZD class members that warrant discussion to enable physicians to make a rational, informed therapeutic choice between the agents. The symposium, 'Are all glitazones the same?', was designed with this purpose. Professor Peter Arner (Huddinge, Sweden) opened the symposium by defining the concept of insulin resistance in association with type 2 diabetes and its complications, focusing particularly on the involvement of free fatty acids as a potential causal factor for insulin resistance. This was followed by a discussion from Professor Hans Hauner (Düsseldorf, Germany) of the mode of action of TZDs, including both *in vitro* and preclinical data. Looking particularly at the potential role of tumour necrosis factor-α, Professor Hauner's presentation provided the rationale for the subsequent clinical presentations of the symposium: Professor Barry Goldstein (Philadelphia, PA, USA) focused on the efficacy of the TZDs, while Professor Harold Lebovitz (Brooklyn, NY, USA) looked at the safety of these agents. Differences in the chemical

structures of the TZD class members may underlie detected differences in the efficacy and safety profiles of troglitazone, rosiglitazone and pioglitazone. The symposium concluded with a discussion by Dr Charles Reasner (San Antonio, TX, USA) in which he considered where TZDs will fit amongst the therapeutic armamentarium available to the physician treating type 2 diabetes [21,24].

From the data presented in this supplement, it is clear that there is variation in our current level of knowledge about the members of the TZD class, largely based on the amount of clinical research that has been performed with each agent. Numerous studies investigating the efficacy and safety of troglitazone, the first TZD to become available on the market in the USA (but subsequently withdrawn), have been published during the past 2 years (reviewed in [25,26]). Many of the clinical data available with the newer agents, rosiglitazone and pioglitazone, are now becoming available as peer reviewed publications rather than published congress presentations.

Overall, the TZDs appear to be similar in their effects on blood glucose; all class members have demonstrated effective glycaemic control, both as monotherapy and in combination with sulphonylureas, metformin or exogenous insulin. The safety profiles of the three agents are more diverse, with what appear to be 'TZD class effects' (probably mediated via activation of PPARγ) and 'TZD-specific effects', which are unique to each agent and may be a consequence of differing chemical structures. Class effects associated with the TZDs include fluid retention, small decreases in haemoglobin and haematocrit and a tendency to weight gain. In terms of unique effects, the elevated incidence of liver failure seen with troglitazone is the most well known [27,28]. As a consequence, this TZD is no longer on the market. A large number of patient-years of clinical safety data with rosiglitazone and pioglitazone have been reviewed by the US Food and Drug Administration (FDA) [29]. They concluded that there was no evidence of hepatotoxicity with either agent, suggesting that the abnormal liver function seen with troglitazone is not a class effect. There is also variation between the three TZD class members in the potential for drug interactions. In this respect, the risk of drug interactions with rosiglitazone appears to be lower than with the two other compounds because it is not metabolised via CYP 3A4 cytochrome isoform.

Summary

The title of this symposium asked the question, 'Are all glitazones the same?'. The answer is undoubtedly 'No'. Indeed, while rosiglitazone and pioglitazone share some class effects with troglitazone, they have several characteristics that define them as unique agents. For example, the three agents differ in their binding affinity for PPARγ – rosiglitazone has a stronger affinity for the receptor than troglitazone or pioglitazone and, as a more 'potent' agent, can exert hypoglycaemic effects at a lower dosage. Furthermore, unlike troglitazone, there has been no liver toxicity associated with the use of rosiglitazone or pioglitazone.

By tackling the control of type 2 diabetes through direct effects on insulin resistance, the TZDs represent an important new therapeutic tool for healthcare professionals. Careful consideration of the data presented during this symposium may help physicians to revisit their management strategies for patients with type 2 diabetes, with special consideration of the potential benefits of the TZDs on risk factors for the secondary cardiovascular complications associated with the condition.

As the chairmen of the symposium, we would like to thank the speakers for their valuable contributions and SmithKline Beecham Pharmaceuticals for their support through an educational grant. The TZDs clearly represent a promising new therapeutic option that may help physicians and their patients with type 2 diabetes to achieve therapeutic goals and prevent late complications of the disease.

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