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Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes

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Abstract

This analysis compares the safety and tolerability of pioglitazone (a thiazolidinedione), metformin (a biguanide), and gliclazide (a sulfonylurea). Data collected from four 1-year, double-blind studies comparing treatment of over 3700 patients with type 2 diabetes with pioglitazone, metformin, or gliclazide have been combined to provide comparative tolerability and safety profiles. All treatments were well tolerated with approximately 6% of patients withdrawing from treatment because of side-effects. The side-effects profile varied between treatments, with pioglitazone being associated with edema, metformin with gastrointestinal side-effects, and gliclazide with hypoglycemia. Cardiovascular outcome was similar with all treatments, with no excess reports of cardiac failure with pioglitazone treatment. Both pioglitazone and gliclazide resulted in mean weight gain, whilst with metformin there was mean weight loss. Mean liver enzyme values decreased with pioglitazone and to a lesser extent with metformin. With gliclazide, mean liver enzyme values increased. The expected small decreases in mean hemoglobin and hematocrit seen with pioglitazone also occurred with metformin and to a lesser degree with gliclazide. The results show that all three drugs are safe, but that tolerability profiles vary. Each treatment provides an alternative therapy for type 2 diabetes, dependent on the particular needs of individual patients.

Keywords: Gliclazide; Metformin; Pioglitazone; Safety and tolerability

1. Introduction

Type 2 diabetes is a disease not only affecting glucose metabolism, but a syndrome involving amongst others, lipid disturbances and abnormal vascular function. The hypothesis first proposed by Reaven [1,2] that insulin resistance is involved in many of these abnormalities, has now gained widespread consensus.

The thiazolidinediones improve both glycemic control and specific elements of dyslipidemia in type 2 diabetes by interacting directly with the peroxisome proliferator gamma receptor to reduce insulin resistance [3]. Despite this, there has been some reluctance to prescribe these agents widely in clinical practice.

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The main reasons for this are concerns about safety of the class. The first agent, troglitazone, was withdrawn from the market because of rare, but serious hepatotoxicity in susceptible patients. In addition, edema occurs in a proportion of patients during treatment with thiazolidinediones. This has led to suggestion that fluid retention may lead to precipitation of heart failure and increased cardiovascular risk in a patient group already compromised [4].

Pioglitazone is one of two thiazolidinediones marketed in Europe shortly after the withdrawal of troglitazone [5]. Although placebo-controlled trials with this compound showed no evidence of hepatotoxicity or increased incidence of congestive heart failure [6], the trials were of relatively short-term duration and direct comparisons with other oral glucose-lowering agents were not possible.

Recently, four large 1-year, double-blind trials comparing the effects of pioglitazone treatment as monotherapy or combination therapy with either a biguanide (metformin) or a sulfonylurea (gliclazide) have been completed [7–10]. Safety data collected from these trials allow comparison of the safety and tolerability profile of pioglitazone with the older, established oral glucose-lowering agents.

2. Research design and methods

The trials were conducted in hospital or general practice centers in Europe, Canada, and Australia and recruited patients aged $\geq$35 and $\leq$75 years with inadequately controlled type 2 diabetes. All patients gave written, informed consent to participate in the study and local Ethics Committee approval was obtained for each site. The study was conducted in accordance with the Declaration of Helsinki and the requirements of Good Clinical Practice of the European Community.

Major exclusion criteria were type 1 diabetes, use of insulin, concomitant congestive heart chronic pancreatitis; familial polyposis coli; malignant disease in the previous 10 years; or myocardial infarction, transient ischemic attacks, or stroke in the previous 6 months. Patients with alanine aminotransferase (ALT) above three times the upper limit of normal (ULN) and serum creatinine $>$ 135 μmol/L were also excluded. Two studies compared pioglitazone, metformin, or gliclazide as monotherapy treatments in patients naïve to oral glucose-lowering therapy (1194 and 1250 patients, respectively) [7,8]. Two others compared combination therapy treatments. In one, pioglitazone or metformin was added to treatment of patients with type 2 diabetes inadequately controlled with a sulfonylurea (639 patients) [9]. In the other, pioglitazone or gliclazide was added to treatment of patients inadequately controlled with metformin treatment (630 patients) [10].

Patients were randomized to treatment after screening and all treatments were blinded to patient and investigator using a double-dummy technique. Treatments were force-titrated, dependent on tolerability, over the first 8–16 weeks to maximum doses of 45 mg of pioglitazone daily, 2550 mg of metformin daily and 320 mg of gliclazide daily. The dose of any medication could not be changed after this titration period. Routine safety data, including adverse events, laboratory variables, electrocardiographs (ECGs), vital signs, and body weight were collected at each of the 2-monthly visits over 1 year. Patients were instructed to adhere to a disease- and weight-orientated diet throughout the study. Dietary advice was given at baseline with the target of body weight normalization and supply of individually appropriate calories and nutrients. If body weight increased more than 5% at any stage or HbA_{1c} increased to greater than 9% after completed dose titration, patients were given further intensive dietary counselling.

To obtain an overview of comparative safety and tolerability, data from individual trials have been combined when clinically appropriate. In all other cases, data from individual trials are presented. Descriptive statistics were used to summarize changes in baseline characteristics, laboratory variables, and the reporting of adverse events. All adverse events were coded according to MedDRA® terminology and were classified according to severity (mild, moderate, or severe) and seriousness (leading to death or permanent disability or requiring hospitalization).

3. Results

3.1. Baseline data

In total, the trials randomized 3713 patients. Demographic data for pioglitazone, gliclazide, and