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Troglitazone

A Review of its Use in the Management of Type 2 Diabetes Mellitus

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Data Selection

Sources: Medical literature published in any language since 1966 on troglitazone, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'troglitazone', 'CI-991', 'CS-045', 'GR-92132' and 'GR-92132X'. Medline and EMBASE search terms were 'troglitazone', 'CI-991', 'CS-045', 'GR-92132', 'GR-92132X' and '97322-887-7'. Searches were last updated 11 February 1999.

Selection: Studies in patients with type 2 diabetes mellitus or impaired glucose tolerance who received troglitazone. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Troglitazone, thiazolidinediones, diabetes mellitus, insulin resistance, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Troglitazone is the first of a new group of oral antidiabetic drugs, the thiazolidinediones, and is indicated for the treatment of patients with type 2 (non–insulin-dependent) diabetes mellitus. Troglitazone acts by enhancing the effects of insulin at peripheral target sites and, unlike the sulphonylurea drugs, is not associated with hypoglycaemia when administered as monotherapy.

Clinical trials with troglitazone (usually 200 to 600 mg/day) in patients with type 2 diabetes mellitus consistently showed marked improvement in glycaemic control, as well as reductions in fasting serum insulin, C-peptide and triglyceride levels. Comparative studies with either glibenclamide (glyburide) or metformin indicated similar glycaemic control with troglitazone or these agents. Serum insulin levels were lower with troglitazone than with glibenclamide. Clinical trials of up to approximately 2 years' duration showed that glycaemic control is maintained with troglitazone on a long term basis.

In general, troglitazone is well tolerated by the majority of patients. However, discontinuation of troglitazone because of elevated liver enzyme levels occurs in approximately 2% of patients receiving the drug, and frequent monitoring of liver enzymes is required (e.g. at least 11 times during the first year of therapy). Among patients who started troglitazone therapy in 1998 (after the incorporation of a boxed warning and increased monitoring requirements in the product labelling), the estimated risk of liver-related death is approximately 1 in 100 000.

Conclusions: Troglitazone improves the ability of target cells to respond to insulin. The drug has been shown to improve glycaemic control in patients with type 2 diabetes mellitus when used as monotherapy or in combination with other oral antidiabetic drugs or insulin, and its efficacy is similar to that of glibenclamide or metformin. Although troglitazone is generally well tolerated, close monitoring of liver enzyme function is required to minimise the rare occurrence of serious hepatic dysfunction. Drug acquisition and liver function monitoring costs, as well as potential adverse effects, are important factors that may ultimately determine the precise place of troglitazone in the management of type 2 diabetes mellitus. Nevertheless, as the first member of a new class of oral antidiabetic agents, the thiazolidinediones, troglitazone offers an effective treatment option in patients with type 2 diabetes mellitus through its action of improving insulin sensitivity.

Overview of Type 2 Diabetes Mellitus

The prevalence of type 2 diabetes mellitus is approximately 5% in North America and Europe, and increases with age. Diabetes mellitus is even more common among certain populations, such as Native North Americans and African Americans. Multiple mechanisms appear to be involved in the pathogenesis of type 2 diabetes mellitus, including impaired insulin secretion by pancreatic β cells, increased hepatic gluconeogenesis, and reduced glucose uptake by skeletal muscle and adipose tissue (peripheral insulin resistance). These effects lead to hypergly-

caemia in the short term, and to micro- and macrovascular complications in the long term. Available evidence suggests that improving glycaemic control reduces the risk of diabetic complications, although this relationship is more clear for microvascular complications such as retinopathy and nephropathy than for macrovascular complications such as coronary heart disease.

Pharmacodynamic Properties and Mechanism of Action

Troglitazone enhances the effects of insulin at peripheral tissue sites (skeletal muscle and adipose tissue), thereby increasing insulin-dependent glucose disposal. Some studies have also shown that troglitazone moderately reduces hepatic glucose production, although this effect has not been consistently demonstrated. Unlike sulphonylurea agents, troglitazone does not directly stimulate the release of insulin from pancreatic β cells. The improved insulin sensitivity demonstrated with troglitazone in patients with type 2 diabetes mellitus was accompanied by improvements in glycaemic control and reduced serum insulin levels. Troglitazone has a significant antihyperglycaemic effect in animal models of both genetic and non-genetic insulin resistance, but not in animal models of insulin deficiency. The mechanism of action of troglitazone at the cellular level has not been fully elucidated. One hypothesis is that binding of troglitazone to peroxisome proliferator-activated receptor-γ (PPARγ) may lead to regulation of the transcription of a number of insulin-responsive genes intimately involved in the control of glucose and lipid metabolism. Other actions may also be involved in the cellular mechanism of troglitazone.

Pharmacokinetic Properties

In healthy volunteers, troglitazone 200 to 600 mg/day achieves peak plasma drug concentrations of 0.9 to 2.8 mg/L approximately 2 to 3 hours after oral administration. It is extensively bound to plasma protein (>99%) and has a steady-state volume of distribution of 2.5 L/kg. The elimination half-life of troglitazone is 9 to 34 hours, allowing for once daily administration of the drug. Troglitazone is extensively metabolised by the liver to 3 main metabolites: the sulphate conjugate (present at a plasma concentration approximately 7 to 10 times that of the parent drug), the quinone metabolite (plasma concentration approximately equal to that of troglitazone) and the glucuronide metabolite (low or negligible plasma concentrations). Animal data indicate that the quinone metabolite has modest pharmacological activity, although the clinical relevance of this finding is unclear. Almost none of an administered dose of troglitazone is eliminated unchanged in the urine.

Therapeutic Use

In clinical trials of patients with type 2 diabetes mellitus, administration of troglitazone, alone or in combination with other antidiabetic agents, was consistently associated with improved glycaemic control compared with placebo or baseline. Statistically and clinically significant reductions were achieved in fasting serum or plasma glucose (FSG or FPG) levels and glycosylated haemoglobin (HbA_{1c}) values. Fasting serum insulin, C-peptide and triglyceride levels were also typically reduced (by 13 to 26% from baseline in the case of triglyceride levels).

In large (n > 100) clinical trials conducted in North America in which troglitazone was administered as monotherapy (typically 200 to 800 mg/day for 12 to 26 weeks), FSG was reduced by approximately 11 to 33% and HbA_{1c} by about 5 to 15% (relative reduction) compared with placebo or baseline values. Although a clear overall dose-response pattern was not evident, troglitazone was consistently effective over its recommended dosage range (200 to 600 mg/day in the US). The effects of troglitazone on glycaemic control were maintained for

≥1 year in a trial in which dosage adjustments were allowed after a 6-month fixed dosage interval. Results of a large study in elderly patients (mean age 75 years) with type 2 diabetes mellitus were similar to those of studies conducted in patients not selected by age. In comparative trials, troglitazone 600 or 800 mg/day had similar efficacy to glibenclamide (glyburide) titrated to response, in terms of glycaemic control, although only troglitazone was associated with reductions in serum insulin levels. Comparisons between troglitazone and metformin in commonly used dosage regimens also showed similar effects on glycaemic control. Results of studies with troglitazone monotherapy conducted in Japan were very similar to those conducted in Europe and North America.

Concomitant treatment with troglitazone 200 to 600 mg/day, plus either glibenclamide 12 mg/day (n = 545) or metformin 1000mg twice daily (n = 28) was more effective at achieving glycaemic control than monotherapy with these drugs. An open-label extension of troglitazone plus glibenclamide therapy demonstrated that glycaemic control was maintained with combined therapy on a long term basis (116 weeks). Other trials of up to 1 year's duration also showed significantly greater reductions in FPG and HbA_{1c} when troglitazone was added to sulphonylurea therapy compared with sulphonylurea monotherapy.

The addition of troglitazone 200 to 600 mg/day to insulin therapy (≥30 U/day) in patients with type 2 diabetes mellitus reduced FSG levels, insulin dosage requirements and HbA_{1c} values, with glycaemic control maintained for up to 23 months in an extension of the largest study (n = 286 for the long term extension).

Tolerability

In clinical trials, the incidence and type of adverse events associated with troglitazone were broadly similar to those observed with placebo. Tolerability data have been pooled from studies conducted in North American patients with type 2 diabetes mellitus receiving troglitazone (n = 1450) or placebo (n = 492). The most frequently reported adverse events with both troglitazone and placebo were infection (18 *vs* 22%), headache (11 *vs* 11%) and pain (10 *vs* 14%). Other adverse events included accidental injury, asthenia, dizziness, back pain, nausea, rhinitis, diarrhoea, urinary tract infection, peripheral oedema and pharyngitis; these were reported in 5 to 8% of troglitazone recipients and 4 to 7% of placebo recipients. The rate of treatment withdrawal during clinical trials was approximately 4% for both troglitazone and placebo. Unlike sulphonylurea drugs, troglitazone is not associated with hypoglycaemic reactions when administered as monotherapy.

Reversible elevations in serum liver enzymes (ALT levels >3 times the upper limit of normal) were noted in 1.9% of patients receiving troglitazone and 0.6% of placebo recipients in North American trials. Since its market launch, troglitazone has been associated with a number of reports of idiosyncratic liver dysfunction which, in a small number of cases, has led to death or the need for liver transplantation. Thus, although approximately 2% of patients receiving troglitazone can be expected to discontinue therapy because of elevated liver enzymes, the overall incidence of permanent liver damage leading to death or liver transplantation is estimated to be about 1 case in every 50 000 to 60 000 patients treated with troglitazone in the US. The manufacturer has introduced a series of labelling changes for the drug, requiring frequent monitoring of liver enzymes (e.g. at least 11 times during the first year of therapy) as well as careful monitoring of clinical signs of liver dysfunction. This appears to have reduced the risk of permanent liver damage: recent estimates focusing specifically on the

risk of death related to liver dysfunction among patients who started troglitazone therapy in the US in 1998 indicate a risk of approximately 1 in 100 000.

Drug Interactions

Troglitazone appears to induce drug metabolism by the cytochrome P450 (CYP) 3A isoenzyme pathway, and concomitant administration with a variety of CYP3A substrates has resulted in decreased plasma concentrations of these drugs. Such substrates include terfenadine, cyclosporin and components of oral contraceptives (ethinylestradiol and norethindrone; potentially leading to loss of contraceptive efficacy). Concurrent administration of troglitazone and cholestyramine is not recommended because cholestyramine markedly reduces the absorption of troglitazone.

Dosage and Administration

Troglitazone is administered orally and should be taken with a meal, since this enhances absorption of the drug. The recommended dosage regimen of troglitazone in the US is 200 to 600mg once daily, with the usual dosage being 400mg once daily. If there is no response to the maximum dosage after 1 month, the drug should be discontinued in favour of alternative therapy. In Japan, the recommended dosage regimen of troglitazone is 200mg twice daily (after meals in the morning and evening).

When troglitazone is added to insulin therapy, it should be initiated at a dosage of 200mg once daily and the current insulin dosage should be continued (but may subsequently need to be reduced depending on glucose-lowering response). The dosage of troglitazone may be increased after 2 to 4 weeks for patients not responding adequately to this combined therapy. Dosage adjustment of troglitazone in patients with renal insufficiency is not necessary. Troglitazone is not recommended in patients with hepatic impairment. All patients receiving troglitazone should be monitored closely for laboratory and clinical signs of liver damage.

Troglitazone (fig. 1) is the first of a new group of oral antidiabetic drugs, the thiazolidinediones, to be marketed. This new structural class acts by decreasing insulin resistance. Thus, troglitazone adds a novel oral treatment option to currently available agents (i.e. sulphonylureas, biguanides and α-glucosidase inhibitors) in the management of patients with type 2 (non–insulin-dependent) diabetes mellitus.

A brief overview of troglitazone was published in *Drugs* in mid-1997.[1] The current article provides a more comprehensive and updated review of the pharmacology, clinical efficacy and tolerability of the drug.

1. Overview of Type 2 Diabetes Mellitus

1.1 Epidemiology and Pathophysiology

In the US alone, there are currently estimated to be about 14 million people with type 2 diabetes mellitus, although the condition is undiagnosed in approximately half of these individuals.[2] This represents about 90% of the total US diabetic population of 16 million; the other 10% have type 1 (insulin-dependent) diabetes mellitus.[2-4] The prevalence of type 2 diabetes mellitus increases with age and varies widely between different populations and ethnic groups. For example, the prevalence among Europeans and US Caucasians is 5 and 7%, respectively,[5] but it may be as high as 20 to 25% among south Asian immigrants aged 35 to 69 years living in the UK.[6] Other populations with a high prevalence of diabetes mellitus include Native North Americans, Pacific Islanders and African Americans.[5] In the US, the prevalence of type 2 diabetes mellitus among individuals over 65 years of age is estimated at 10%,[7] which is approximately twice the prevalence for the overall US population. The worldwide prevalence of type 2 diabetes mellitus is steadily increasing, primarily

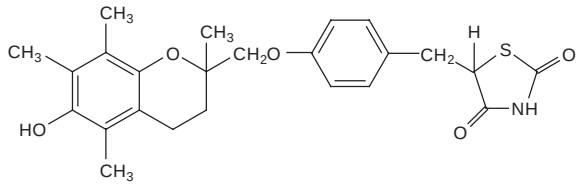

Fig. 1. Chemical structure of troglitazone.

because of increased obesity, an aging population, decreased physical activity and the adoption of a Western lifestyle by people in underdeveloped nations. Within two decades there will be an estimated 250 million people globally with this condition.[4,8,9]

Type 2 diabetes mellitus is a heterogeneous disorder, with both genetic and environmental factors contributing to its development.[8,10,11] The pathogenesis of type 2 diabetes mellitus involves multiple mechanisms leading to hyperglycaemia, most notably increased hepatic glucose production, impaired insulin secretion by pancreatic β cells and reduced glucose uptake by skeletal muscle and adipose tissue (peripheral insulin resistance).[12] Although it is not clear which is the primary contributory mechanism, peripheral insulin resistance may have a pivotal role in the development of hyperglycaemia in patients with type 2 diabetes mellitus and in prediabetic individuals with impaired glucose tolerance (IGT). Indeed, peripheral insulin resistance can be detected even before deterioration of glucose tolerance occurs, and is often accompanied by a compensatory increase in insulin secretion. Eventually, however, pancreatic β cells are no longer able to compensate by secreting sufficiently increased amounts of insulin. Glucose-induced insulin secretion subsequently falls and glucose homeostasis deteriorates, ultimately leading to overt type 2 diabetes mellitus.

1.2 Complications of Diabetes and the Value of Tight Glycaemic Control

In a significant proportion of patients, type 2 diabetes mellitus may remain undiagnosed for several years before overt symptoms appear, and many patients show evidence of diabetic complications at diagnosis. Chronic complications of diabetes mellitus affect various organ systems and can be broadly categorised as macrovascular and microvascular.

Macrovascular complications involve large blood vessels and are manifested as coronary heart disease (CHD), stroke and peripheral vascular disease.[13] In patients with diabetes mellitus, large blood vessels become more susceptible to occlusion. This may be as a direct result of chronic hyperglycaemia or indirectly from accompanying hypertension and changes in serum lipid levels, specifically increased low density lipoprotein (LDL)-cholesterol and triglyceride levels and lower levels of high density lipoprotein (HDL)-cholesterol.[13,14] Long term complications such as CHD appear to be accelerated by the interaction between diabetes mellitus and other comorbid conditions. For any given level of elevated serum cholesterol, the presence of diabetes mellitus increases the risk of CHD by approximately 3-fold, and the overall risk of CHD morbidity and mortality among patients with diabetes mellitus is about 2 to 3 times that of the general population.[15]

Microvascular complications of diabetes mellitus increase with the progression of the disease and appear to be related to the degree and duration of hyperglycaemia.[13,16] Abnormalities of arterioles and capillaries develop, causing leaky vessel walls, membrane thickening and functional impairment of the vessels, ultimately leading to diabetic nephropathy, retinopathy and neuropathy.

Long-awaited data from the United Kingdom Prospective Diabetes Study (UKPDS) were re-

cently published and provide some key outcomes-based evidence supporting the value of tight glycaemic control in patients with type 2 diabetes mellitus.[17,18] In particular, results of UKPDS-33,[17] a randomised long term study which involved 3867 newly diagnosed patients with type 2 diabetes followed for 10 years, demonstrated that intensive therapy (with diet and drugs; troglitazone was not used in this study) significantly reduced the incidence of microvascular complications by 25% ($p < 0.01$) compared with conventional therapy (primarily with diet). Microvascular complications were defined as retinopathy requiring photocoagulation, vitreous haemorrhage and/or fatal or non-fatal renal failure. Intensive treatment produced no statistically significant effects on macrovascular complications, diabetes-related mortality or overall mortality in UKPDS-33. Nevertheless, these results have largely put to rest concerns raised by the University Group Diabetes Program[19] several years ago that sulphonylureas may actually produce worse cardiovascular outcomes than placebo. Beneficial effects on mortality and micro- and macrovascular complications were observed in obese patients with type 2 diabetes mellitus treated with metformin in UKPDS-34,[18] although some concerns have been raised[20] about the design of this trial.

Until data from the UKPDS became available, the most convincing evidence for the value of tight glycaemic control came from the Diabetes Control and Complications Trial (DCCT). This study was conducted in highly motivated, relatively young patients with type 1 diabetes mellitus receiving intensive insulin therapy.[21] Results of the DCCT demonstrated that the onset of nephropathy, retinopathy and neuropathy was delayed, and progression of these microvascular complications was slowed, over a 9-year period (mean follow-up 6.5 years) in patients receiving intensive treatment regimens compared with those receiving conventional treatment regimens. The 50 to 75% risk reduction for development or progression of these complications correlated with the reduction in glycosylated haemoglobin (HbA_{1c}) achieved by intensive treatment, strongly suggesting that tight glycaemic control prevents these complications.

2. Pharmacodynamic Properties and Mechanism of Action

Troglitazone improves insulin sensitivity at peripheral tissue sites (skeletal muscle and adipose tissue), resulting in increased insulin-dependent glucose disposal.[12,22,23] Since the mechanism of action of troglitazone has not been fully elucidated, it is unclear whether improved insulin sensitivity reflects a direct effect of troglitazone or an indirect action of the drug secondary to changes in other metabolic parameters (see section 2.1). Although data are not clearly consistent, troglitazone also appears to moderately reduce hepatic glucose production, albeit to a lesser extent than the biguanide metformin (see section 2.3). Unlike sulphonylurea drugs, troglitazone does not directly stimulate pancreatic β cells to increase insulin secretion. In patients with type 2 diabetes mellitus, the improved insulin sensitivity produced by troglitazone results in reductions in plasma glucose, HbA_{1c} and insulin levels (see section 4.1).

2.1 Cellular Mechanism of Action

The precise mechanism of action of troglitazone at the cellular level has not been fully elucidated. One hypothesis, which is supported by a variety of experimental data, involves binding of troglitazone to a nuclear receptor (peroxisome proliferator-activated receptor-γ; PPARγ) which is found primarily, but not exclusively, in adipose tissue.[12,23,24] PPARγ regulates the transcription of a number of insulin-responsive genes intimately involved in the control of glucose and lipid metabolism. For example, PPARγ activation induces the expression of various genes involved in fatty acid uptake in adipose tissue without affecting their expression in muscle tissue, potentially leading to depletion of fatty acids in muscle and, in turn, whole body glucose homeostasis.[24] Activation of PPARγ may also lead to alterations in glucose homeostasis via modifications of adipocyte-derived signalling molecules, which affect muscle glucose metabolism.

The PPARs are a family of transcription factors (PPARα, γ and δ have been identified thus far) and the specific roles of each of these receptors have not yet been fully determined. For example, we do not know the metabolically relevant genes that are directly modulated by PPARγ as activated by troglitazone. Nevertheless, PPARγ appears to be the most likely candidate for a thiazolidinedione receptor,[12] since these drugs have a high affinity for PPARγ *in vitro*.[25] Moreover, a comparison of troglitazone and other thiazolidinediones indicates a correlation between PPARγ binding affinity and *in vivo* antidiabetic activity of these drugs.[26,27] The suggestion that transcriptional modifications are involved in the actions of troglitazone is supported by the temporal association between drug administration and improvements in insulin sensitivity; typically, several days of therapy are required before an effect is observed,[23] and often, several weeks of therapy are required to see the full effect of troglitazone.[28-31]

A schematic representation of the PPARγ hypothesis of the mechanism of action of troglitazone is presented in figure 2.[12,23] However, it is important to note that the PPARγ hypothesis can not explain all effects of troglitazone on glucose metabolism that have been found under experimental conditions. Nuclear receptors other than the PPARs may also have a role in the action of thiazolidinediones on glycaemic control and lipid metabolism.[12] In addition, various preclinical studies have demonstrated acute (and therefore PPARγ-independent) actions of troglitazone on glucose metabolism.[32-37] For example, troglitazone acutely increased basal and insulin-stimulated glucose uptake in muscle strips from Sprague-Dawley rats.[33] Thus, it remains unclear whether improved insulin sensitivity associated with troglitazone in patients with type 2 diabetes mellitus reflects a direct effect of troglitazone or an indirect action of the drug secondary to changes in other metabolic parameters (e.g. circulating free fatty acids, etc.), or perhaps a combination of both.

Troglitazone exerts additional effects at the cellular level which may prove to be clinically relevant. These include an antagonistic effect on tumour necrosis factor-α (TNF-α), a cytokine which may be implicated in the development of obesity-linked insulin resistance and type 2 diabetes mellitus,[38] and an inhibitory effect on oxidation of LDL[39] (oxidised LDL is thought to be associated with atherogenesis[40]). Additional data indicate that troglitazone also reduces the production of TNF-α and other inflammatory cytokines, and may affect the expression of some adhesion molecules which play a key role in the recruitment of monocytes and the formation of foam cells, thereby having potential to prevent atherosclerosis.[41] Indirect evidence suggests that troglitazone may even have a role as a regulator of gene expression during atherogenesis, since ligand activation of PPARγ in myelomonocytic cells promotes the uptake of oxidised LDL.[42,43] Troglitazone might also have an anti-inflammatory effect, as demonstrated by a scavenging effect on reactive oxygen species pro-

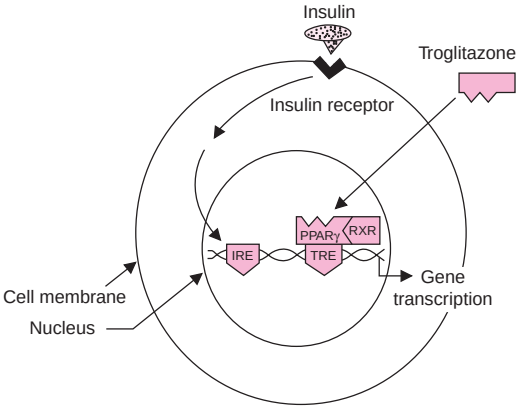

Fig. 2. Schematic representation of the PPARγ hypothesis of the mechanism of action of troglitazone. Binding of troglitazone to PPARγ, which exists as a heterodimer with retinoic acid X receptor (RXR), may lead to regulation of the transcription of a number of insulin-responsive genes intimately involved in the control of glucose and lipid metabolism.[12,23] Importantly, the PPARγ hypothesis cannot explain all effects of troglitazone on glucose metabolism that have been found under experimental conditions, and nuclear receptors other than the PPARs may also have a role in the action of thiazolidinediones. **IRE** = insulin-responsive element; **PPARγ** = peroxisome proliferator-activated receptor γ; **TRE** = thiazolidinedione-responsive element.

duced by xanthine-xanthine oxidase and generated by stimulated neutrophils.[44]

Results from several of these *in vitro* studies are supported by results of *in vivo* studies in animals[45] and *ex vivo* data from humans.[46-48] For example, Cominacini and colleagues demonstrated a statistically significant reduction in susceptibility of LDL to oxidation in healthy volunteers receiving troglitazone 400mg twice daily for 2 weeks compared with placebo,[46] and with a lower dose of troglitazone (200mg once daily) in an 8-week placebo-controlled study in patients with type 2 diabetes mellitus.[47] Similar results were achieved with troglitazone 400 mg/day in obese individuals,[48] and together these data suggest a potentially beneficial effect of the drug on attenuating the development of atherosclerosis by modifying LDL-related events. Cominacini and colleagues[47] also demonstrated a statistically significant reduction in plasma E-selectin levels after 8 weeks of troglitazone 200 mg/day compared with placebo in patients with type 2 diabetes mellitus. E-selectin is an adhesion molecule which may serve as a molecular marker for atherosclerosis and the development of CHD.[49]

2.2 Animal Models of Diabetes Mellitus

In animal models of genetic insulin resistance (e.g. the KKA, *ob/ob* and *db/db* mouse; the Zucker *fa/fa* rat), troglitazone significantly reduced plasma glucose, insulin and triglyceride levels.[32,50-52] Likewise, troglitazone had a marked antihyperglycaemic effect in models of non-genetic insulin resistance (e.g. the fructose-fed and high fat diet-adapted rat).[52-55] However, in a model of insulin deficiency (the streptozotocin-induced diabetic rat), plasma glucose levels were not affected by troglitazone[51,56,57] unless exogenous insulin was administered concomitantly[57] or pancreatic islet cells were transplanted into the animals.[56] Insulin sensitivity was improved in this model during hyperinsulinaemic euglycaemic clamp studies, as demonstrated by a reduction in hepatic glucose output (probably via a decrease in gluconeogenesis) and an increased glucose infusion rate.

Plasma glucose levels were also unaffected by troglitazone in normoglycaemic animals.[50] Thus, despite a marked effect on improving insulin sensitivity, hypoglycaemia does not occur with troglitazone in euglycaemic animal models because of the negative feedback systems between serum glucose and insulin levels: as insulin resistance improves, a corresponding reduction in insulin secretion occurs. In contrast, sulphonylureas and, of course, insulin itself have considerable hypoglycaemic activity.[12]

Troglitazone has effects on pancreatic islet cells in animal models (such as regranulation leading to restoration of cellular insulin content in diabetic *db/db* mice[58]); however, whether such effects reflect a direct or an indirect action of troglitazone is not clear.[23] Proposed mechanisms for this putative effect of the drug on pancreatic β cell function include a direct action on the β cell, adaptive changes to the increase in insulin sensitivity, alterations in the prevailing serum glucose levels, or a combination of these factors.[59]

2.3 Metabolic Studies of Insulin Sensitivity and Glucose Turnover in Patients

Significant improvements in glucose disposal were observed in patients with type 2 diabetes mellitus receiving troglitazone 400 or 600 mg/day for up to 6 months.[60-62] In some,[61,62] but not all,[60] of the trials, a moderate reduction in basal hepatic glucose production was also demonstrated, at least with some troglitazone dosage regimens. A hyperinsulinaemic euglycaemic clamp technique was used in these metabolic evaluations and involved intravenous administration of both insulin and glucose to achieve a preselected stable plasma glucose level (i.e. the amount of glucose infused to counter the effects of exogenous insulin provided an indication of insulin sensitivity).

In the largest trial, Maggs et al.[61] demonstrated an increase in glucose disposal rate of approximately 45% from baseline among 93 patients with type 2 diabetes mellitus receiving troglitazone 400 or 600 mg/day for 6 months ($p = 0.003$), and hepatic glucose production was moderately sup-

pressed with troglitazone 600 mg/day compared with placebo ($p = 0.02$). Likewise, 11 patients with type 2 diabetes mellitus showed a marked improvement in glucose disposal (41 to 63% increase *vs* baseline; $p < 0.01$) and a moderate reduction in basal hepatic glucose production (by 17% *vs* baseline; $p < 0.05$) after 6 to 12 weeks of treatment with troglitazone 400 mg/day.[62] In both of these studies, improved insulin sensitivity and reduced hepatic glucose production associated with troglitazone therapy were accompanied by improvements in glycaemic control and reduced serum insulin levels.

Comparisons of the metabolic effects of troglitazone and metformin in patients with type 2 diabetes mellitus showed a much more marked increase in glucose disposal with troglitazone but a somewhat greater reduction in endogenous glucose production with metformin.[60] 29 patients were randomised to receive either troglitazone 400mg once daily or metformin 1000mg twice daily for 3 months, followed by combined therapy with both drugs for a further 3 months. After 3 months of troglitazone therapy, glucose disposal rate was increased by 54% from baseline [9.5 *vs* 14.7 mmol/m^2 body surface area (BSA) per minute; $p = 0.006$] compared with a 13% increase with metformin (13.3 *vs* 15.1 mmol/m^2 BSA per minute; $p = 0.03$), and the difference between treatment groups was statistically significant ($p = 0.03$). Metformin was associated with a 19% reduction in endogenous glucose production ($p = 0.001$ *vs* baseline) compared with a nonsignificant 3% decline with troglitazone ($p = 0.04$ for the between group comparison). After the first 3 months of treatment, similar marked improvements in glycaemic control were observed in both treatment groups, and further improvements were seen with combined therapy.

Significant improvements in glucose tolerance and insulin resistance were also demonstrated with troglitazone 200mg twice daily for 12 weeks in a placebo-controlled study of 18 nondiabetic obese patients, 9 of whom had IGT.[63] In this analysis, an insulin sensitivity index was calculated from results of the hyperinsulinaemic euglycaemic clamp studies. At the lower, more physiological, rate of insulin administration used in the study (40 mU/m^2 BSA per minute), the insulin sensitivity index was increased by approximately 75% with troglitazone, from a value of 1.6 at baseline to 2.8 at the end of the treatment period ($p = 0.007$). Troglitazone significantly improved glucose disposal rates from 4.7 to 6.0 mg/kg/min ($p = 0.004$) and from 9.0 to 9.9 mg/kg/min ($p = 0.02$) with insulin infusions of 40 and 300 mU/m^2 BSA per minute, respectively. Glucose disposal and insulin sensitivity were essentially unchanged among placebo recipients.

3. Pharmacokinetic Properties

Table I summarises the main pharmacokinetic properties of troglitazone. The drug has a sufficiently long elimination half-life ($t_{½\beta}$; 9 to 34 hours)[64-67] to allow for once daily administration. (Japanese data indicate a $t_{½\beta}$ at the lower end of this range, and the drug is administered on a twice daily basis in that country.[66]) Peak plasma drug concentrations are achieved 2 to 3 hours after oral administration of troglitazone[65,66,68] and the drug is extensively bound to plasma protein (>99%).[65,69,70]

Peak plasma troglitazone concentrations (C_{max}) [0.9 to 2.8 mg/L] and area under the plasma concentration-time curve (AUC) [7.4 to 22.1 mg/L · h] values at steady state increased dose-proportionally with administration of troglitazone 200 to 600 mg/day in a group of 21 healthy US volunteers.[65] Steady state plasma concentrations of the drug are achieved after 3 to 5 days[65] and recent data indicate that the volume of distribution of troglitazone at steady state is 2.5 L/kg[64] (which is markedly lower than values previously reported[65]). C_{max} and AUC values also increased dose-proportionally in a small group of healthy Japanese volunteers receiving single oral doses of troglitazone 10 to 800mg.[66] In this analysis, troglitazone 200mg was associated with a C_{max} and AUC of 0.5 mg/L and 4.4 mg/L · h, respectively.

In Japanese patients with type 2 diabetes mellitus, mean plasma troglitazone concentrations at steady state ranged between 0.4 and 1.2 mg/L after administration of troglitazone 400 mg/day for 6

Table I. Pharmacokinetic properties of troglitazone after oral administration to healthy volunteers[64-66]

t_{max}	2 to 3h[a]
$t_{½β}$	9 to 34h
C_{max} (200, 400, 600 mg/day)	0.9, 1.6, 2.8 mg/L[a]
AUC (200, 400, 600 mg/day)	7.4, 13.4, 22.1 mg/L • h[a]
Plasma protein binding	>99%
Vd	2.5 L/kg[a]
Metabolism	Extensive hepatic metabolism primarily to a sulphate conjugate and quinone metabolite
Elimination	85% of a radiolabelled dose detected in faeces, 3% in urine (primarily as glucuronide conjugate)

a Mean values at steady state.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma drug concentration; **t_{max}** = time to achieve C_{max}; **$t_{½β}$** = elimination half-life; **Vd** = volume of distribution.

weeks.[71] In a US study of 12 patients with type 2 diabetes mellitus receiving troglitazone 400mg once daily, steady state pharmacokinetic parameters were: C_{max} 1.5 mg/L, time to C_{max} 3.25 hours, AUC 15.6 mg/L • h and $t_{½β}$ 23.5 hours.[68]

Troglitazone undergoes extensive hepatic metabolism to 3 main metabolites: the sulphate conjugate (present at a plasma concentration approximately 7 to 10 times that of the parent drug), the quinone metabolite (plasma concentration approximately equal to that of troglitazone) and the glucuronide metabolite (low or negligible plasma concentrations).[64,65,68] Steady state concentrations of the sulphate conjugate of troglitazone (major metabolite) and the quinone metabolite were achieved within 5 days of daily administration of troglitazone 400mg in 12 patients with type 2 diabetes mellitus and in 12 healthy volunteers.[68] No accumulation of troglitazone or its metabolites occurred during 12 weeks of treatment with troglitazone 800 mg/day in 11 patients with diabetes mellitus.[67]

After oral administration of [^{14}C]troglitazone, 85% of the radiolabelled dose was detected in the faeces and 3% in the urine.[65] Essentially no unchanged troglitazone was detected in the urine; the glucuronide metabolite contributed almost all of the urinary radioactivity. Animal data suggest that the sulphate metabolite is pharmacologically inactive and the quinone metabolite has modest activity; the clinical relevance of these findings is not known.[68]

In patients with moderate to severe liver dysfunction, AUC values of the sulphate conjugate were approximately 400% higher, and those of the quinone metabolite were approximately 50 to 150% higher, than in healthy individuals with normal hepatic function.[72] The clinical significance of the reduced capacity to eliminate troglitazone metabolites in patients with hepatic insufficiency is unclear, but troglitazone is not recommended for use in this patient population (see sections 5.2 and 7).

Age does not have a clinically significant effect on the pharmacokinetics of troglitazone, according to results of an analysis of 12 young (aged 18 to 40 years) and 11 elderly (aged 70 to 85 years) healthy volunteers.[67] After administration of troglitazone 800 mg/day for 2 weeks, respective pharmacokinetic parameters for the 2 age groups were C_{max} 2.40 and 2.43 mg/L, AUC 12.5 and 15.6 mg/L • h, and $t_{½β}$ 13.9 and 14.7 hours.

Food has been reported to increase the extent of absorption of troglitazone by 30 to 85%, and the US prescribing information for troglitazone suggests that the drug be taken with a meal to enhance systemic drug availability.[65] Results of a UK crossover study of 12 healthy volunteers are in general agreement with this degree of enhanced absorption.[73] Compared with the fasting state, troglitazone AUC values were 59% greater and C_{max} values were more than 70% higher when the drug (400mg) was taken with or after food. In contrast, a Japanese study showed that AUC values of troglitazone were unaffected by concomitant food intake.[66]

4. Therapeutic Use

Troglitazone is indicated for use in patients with type 2 diabetes mellitus (section 4.1) but has also been evaluated in patients with IGT (section 4.2), a small proportion of whom can be expected to progress to overt type 2 diabetes mellitus each year.

Patients with other conditions thought to be associated with insulin resistance, including polycystic ovary syndrome[74,75] and Werner's syndrome,[76,77] have benefited from troglitazone therapy, although these topics are beyond the scope of this review.

4.1 Therapeutic Use in Patients with Type 2 Diabetes Mellitus

Troglitazone has been evaluated in patients with type 2 diabetes mellitus, both as monotherapy and in combination with either oral antidiabetic agents (e.g. sulphonylureas) or insulin. Most trials of troglitazone monotherapy involved patients with type 2 diabetes inadequately controlled by diet alone (or by diet and sulphonylurea but the sulphonylurea was discontinued during a washout period). Combined therapy was essentially 'add on' therapy and involved patients with inadequate glycaemic control despite dietary and pharmacological treatment. Inadequate glycaemic control was typically defined as fasting plasma or serum glucose (FPG or FSG) levels between 7 and 15 mmol/L (126 and 270 mg/dl). Most of the larger studies (n > 100) were multicentre, double-blind, randomised, placebo-controlled dose-finding trials, typically of 12 to 26 weeks' duration. Thus, clinical evaluation of troglitazone was conducted in a number of well-designed large trials of reasonable duration.

In the majority of trials, the primary end-point was glycaemic control determined as HbA_{1c} at the end of the study period. HbA_{1c} generally reflects the state of glycaemia over the preceding 8 to 12 weeks.[78] Secondary end-points included FSG (or FPG) and serum levels of insulin, C-peptide and lipids or lipoproteins. Measuring these intermediate end-points is appropriate because elevated fasting plasma insulin levels are characteristic in patients with insulin resistance, and epidemiological data (from individuals without diabetes mellitus) suggest that hyperinsulinaemia is a risk factor for CHD.[79] In addition, available data suggest that poor glycaemic control and dyslipidaemia are risk factors for long term complications of diabetes mellitus.[80] C-peptide, which has no known biological action, is formed during cleavage of insulin from proinsulin and is released from pancreatic β cells in equimolar amounts with insulin.[78] Thus, serum C-peptide levels provide an indirect measurement of endogenous insulin.

In general, patients ranged in age from about 40 to 75 years, although a few studies evaluated troglitazone specifically in elderly patients with type 2 diabetes mellitus.[81-83] Patients were well matched in terms of baseline values of FSG and HbA_{1c}, as well as other relevant parameters.

4.1.1 Effects of Monotherapy on Glycaemic Control

Several studies evaluating troglitazone monotherapy in patients with type 2 diabetes mellitus have been conducted in North America and Europe[28-31,59,61,62,81,82,84-93] as well as in Japan.[94-104] Many of the Japanese trials also included at least some patients who received concomitant sulphonylurea therapy (and for this reason, these data will be dealt with separately).[94,97,99-101] A wide range of troglitazone dosage regimens were evaluated, typically 200 to 800 mg/day in 1 or 2 divided daily doses, in trials lasting 12 weeks to 1 year.

North American and European Studies

Results of large (n > 100) placebo-controlled trials of troglitazone monotherapy conducted in North America or Europe are summarised in table II, and data from a representative study are presented in figure 3. In virtually all of these trials, troglitazone significantly reduced FSG and HbA_{1c}, indicating improved glycaemic control. Compared with placebo or baseline values, troglitazone (≥200 mg/day) reduced FSG by approximately 11 to 33% and HbA_{1c} by about 5 to 15% (relative reduction). Fasting serum insulin levels were also typically reduced (by as much as 35%) as were concomitant C-peptide levels. Most of the results presented in table II reflect the effects of troglitazone on glycaemic control relative to placebo. The magnitude of these effects typically comprised a modest worsening of glycaemic control with placebo and an improvement with troglitazone.

All of the trials outlined in table II evaluated a range of dosage regimens over a period of 12 to 26 weeks. Although a clear dose-response pattern was

Table II. Large (n > 100) placebo-controlled dose-finding trials conducted in North America and Europe of troglitazone (T) monotherapy in patients with type 2 diabetes mellitus[a]

Reference	Study design [duration; wk]	Dosage regimen (mg) [no. of patients evaluated]	Effect on FSG (% reduction *vs* PL)	Effect on HbA_{1c} (% relative reduction *vs* PL)	Effect on serum insulin levels (% reduction *vs* PL)
Corrêa et al.[28]	mc, db, r [12]	T 200 bid [47]	15.6**	5.2	22.9**
		T 200 tid [50]	22.3**	7.8*	23.8**
		T 400 bid [47]	24.7**†	10.4**	33.6**†
		PL [49]			
Fonseca et al.[29]	mc, db, r [26]	T 100 od [78]	11.0[b]	(1.4)[b,c]	NA
		T 200 od [81]	21.2*[b]	5.6[b]	NA
		T 400 od [76]	25.8*[b]	9.7*[b]	NA
		T 600 od [79]	30.3*[b]	15.3*[b]	NA
		PL [79]			
Kumar et al.[30]	mc, db, r [12]	T 200 od [48]	17.8**	8.8**	9.2
		T 400 od [41]	14.7**	7.5	20.2*
		T 600 od [47]	19.4**	10.0*	21.1**
		T 800 od [50]	24.8**	12.5*	15.6*
		T 200 bid [45]	19.4**	11.3**	9.2
		T 400 bid [49]	27.9**	11.3*	25.7**
		PL [48]			
Kumar et al.[82][d]	mc, db, r [12]	T 400 od [45]	20.9**	NA	26.0**
		T 200 bid [54]	14.0**	NA	33.1**
		T 800 od [40]	30.2**	NA	35.4**
		T 400 bid [40]	32.6**	NA	34.6**
		PL [45]			
Leutenegger et al.[31]	mc, db, r [16]	T 10 od [54]	1.5	0	(8.4)[c]
		T 30 od [59]	8.3*	1.2	6.0
		T 100 od [55]	9.8*	2.4	6.0
		T 200 od [59]	18.0**	7.3*	10.8
		PL [57]			
Valiquette et al.[92][e,f,g]	NA [12]	T 200 od [792[h]]	11	NA	5
		T 400 od	14	NA	20
		T 600 od	15	NA	18
		T 800 od	19	NA	21
		PL	(6)[c]	NA	4

a All results reflect mean values at the end of the treatment period; means were adjusted for baseline and investigator centre for comparisons with placebo.

b FSG and HbA_{1c} values at 6 months with placebo were estimated using weighted means, and reductions with some troglitazone dosages were estimated from a graph.

c Increase.

d Study conducted in elderly patients only (mean age ≈75 years).

e Study published as an abstract.

f Results reflect change *vs* baseline.

g p values not available.

h Total number of patients in study.

bid = twice daily; **db** = double-blind; **FSG** = fasting serum glucose level; **HbA_{1c}** = glycosylated haemoglobin level; **mc** = multicentre; **NA** = data not available; **od** = once daily; **PL** = placebo; **r** = randomised; **tid** = 3 times daily; **wk** = weeks; * $p < 0.05$, ** $p < 0.001$ *vs* PL; † $p < 0.05$ *vs* T 200 bid.

not evident in many of the studies, the minimum effective dosage of troglitazone for establishing glycaemic control in patients with type 2 diabetes mellitus appears to be 200mg once daily.[31] Few, if any, differences in efficacy were noted between regimens in which the total daily troglitazone dosage was divided into 1, 2 or 3 doses.[28,30,81,82] In general, troglitazone improved glycaemic control across its recommended dosage range of 200 to 600 mg/day (although several studies also included a treatment arm of 800 mg/day; see table II). This was recently confirmed using a dose-response model of metabolic control in patients with type 2 diabetes mellitus, which established that troglitazone 200 to 600mg once daily can be considered the therapeutic dosage range that significantly improves metabolic control in this patient population.[105] The effects of troglitazone 200 to 600 mg/day on glycaemic control were maintained for ≥1 year in a long term trial in which dosage adjustments were allowed after a 6-month fixed dosage interval.[93]

Troglitazone has also been evaluated in a large study of 224 elderly (mean age 75 years) patients with type 2 diabetes mellitus.[82] Troglitazone 400 or 800 mg/day was administered in 1 or 2 divided daily doses for 12 weeks. Results were very similar to those of studies conducted in patients not selected by age: troglitazone reduced FSG by 14 to 33% compared with placebo ($p < 0.001$), and significant reductions were also noted in fasting plasma insulin levels (table II).

Comparisons with Other Oral Agents. In an open-label randomised study comparing troglitazone 800mg once daily and glibenclamide titrated to optimum effect (study stated 'up to 20mg q.d. or b.i.d'), both drugs were effective at reducing FSG at all time-points during the 48-week trial (fig. 4a; table III).[85] Improved glycaemic control associated with troglitazone was accompanied by reductions in total serum insulin levels, whereas modest increases in serum insulin levels were noted with glibenclamide (fig. 4b). These results reflect differences between the 2 drugs in their mechanism of action: troglitazone reduces insulin resistance and the demand for insulin production, whereas sulphonylureas such as glibenclamide stimulate pancreatic β cells to produce higher levels of insulin. It is noteworthy that 23% (18/77) of patients with type 2 diabetes mellitus who were randomised to receive troglitazone withdrew from the study because of lack of efficacy (the majority during the first 12 weeks) compared with only 4% (3/77) of those randomised to glibenclamide treatment; the study was not specifically designed to evaluate glycaemic control, since it focused on cardiac parameters. Among other effects, troglitazone was associated with a statistically significant 5 to 6mm Hg reduction in diastolic blood pressure (DBP), whereas DBP was unaffected by glibenclamide.

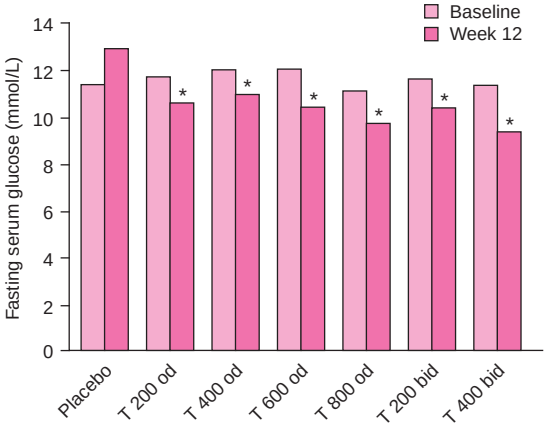

Fig. 3. Changes in mean fasting serum glucose (FSG) levels among 328 patients with type 2 diabetes mellitus randomised to receive troglitazone (T) 200 to 800 mg/day or placebo for 12 weeks in a double-blind randomised trial.[30] **bid** = twice daily; **od** = once daily; * $p < 0.001$ *vs* placebo after adjustment for baseline values.

Two additional studies, both published as abstracts, have compared troglitazone 100, 200 or 600mg once daily with 'optimally titrated' doses of glibenclamide[84] or metformin[89] in patients with type 2 diabetes mellitus (table III). Preliminary data from these large trials indicate similar efficacy between troglitazone 600 mg/day and the comparators in terms of glycaemic control after 26 weeks of therapy, although only troglitazone was associated with lower serum insulin levels. How-

ever, results of a small randomised study comparing troglitazone 400mg once daily and metformin 1g twice daily for 3 months showed only slight nonsignificant reductions in plasma insulin levels in both treatment groups, despite significant reductions in FPG levels of approximately 20% from baseline.[60]

Japanese Studies

Unlike studies conducted in North America and Europe, many of the Japanese monotherapy trials included at least some patients who received concomitant sulphonylurea therapy. Nevertheless, results of studies with troglitazone monotherapy conducted in Japanese patients with type 2 diabetes mellitus were not markedly different from those conducted in patients in Europe and North America. In a 12-week double-blind multicentre trial, Iwamoto and colleagues[98] demonstrated markedly better glycaemic control among 136 patients randomised to receive troglitazone 200mg twice daily than among 126 placebo recipients. Baseline FPG levels were 10.1 mmol/L in both groups, decreasing to 8.8 mmol/L in the troglitazone group and to 9.9 mmol/L in the placebo group ($p < 0.001$ for troglitazone *vs* baseline and placebo). HbA_{1c} decreased from a baseline value of 8.6% to approximately 8.1% after 12 weeks of troglitazone therapy, whereas HbA_{1c} values among placebo recipients remained unchanged at approximately 8.5% ($p < 0.001$ for troglitazone *vs* baseline and placebo). In another large study of 204 patients (without a placebo control group),[99] FPG declined from 10.7 mmol/L at baseline to 8.6 mmol/L after 12 weeks of treatment with troglitazone 200 or 400 mg/day ($p < 0.01$), and corresponding values for HbA_{1c} were 8.9 and 8.1% ($p < 0.01$). Similar results were achieved in a number of smaller studies ($n < 30$) in which Japanese patients with type 2 diabetes mellitus received troglitazone 400 mg/day in 1 or 2 divided daily doses for 8 to 12 weeks[96,97,100-103]

In a long term study in which 57 patients received monotherapy with troglitazone 200 to 800 mg/day for 1 year,[94] FPG levels were reduced from 10.2 mmol/L at baseline to significantly lower levels ranging from 7.6 to 8.3 mmol/L between weeks 16 and 52. HbA_{1c} values declined from 8.7% at baseline to significantly lower values ranging from 7.0 to 7.3% between weeks 16 and 52. In a separate 16-week study by the same investigators,[95] no marked additional effect on glycaemic control was observed when troglitazone dosage was increased from 400 to 800 mg/day.

Kuzuya et al.[106] recently analysed 10 Japanese studies of troglitazone involving a total of 604 patients with type 2 diabetes mellitus, in an effort to determine baseline characteristics affecting the efficacy of the drug. In all of the trials, troglitazone

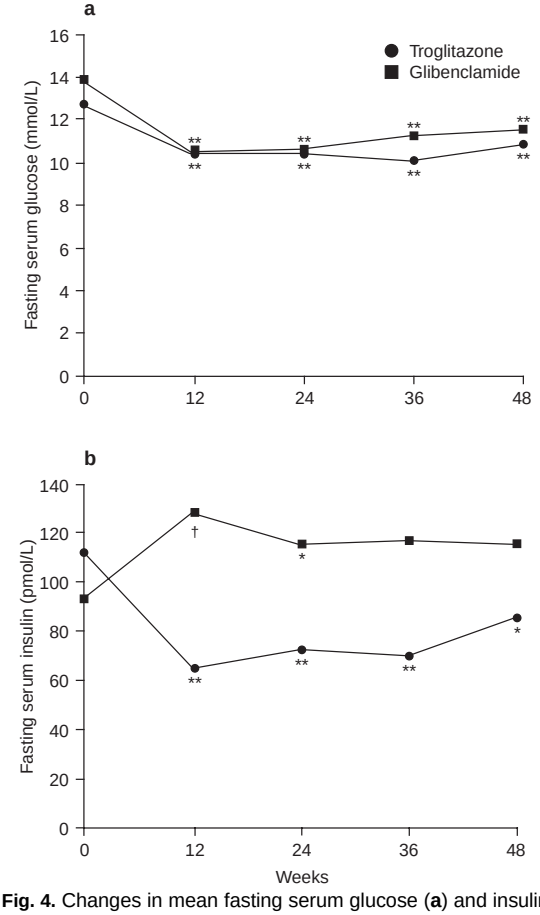

Fig. 4. Changes in mean fasting serum glucose (**a**) and insulin (**b**) levels among 114 patients with type 2 diabetes mellitus. Patients were randomised to receive troglitazone 800 mg/day or glibenclamide (glyburide) titrated to response in an open-label multicentre trial.[85] * $p < 0.05$; † $p < 0.01$; ** $p < 0.001$ *vs* baseline.

was administered at a dosage of 400 mg/day for 12 to 16 weeks. Results of the evaluation indicated that the reduction in FPG with troglitazone was positively correlated with a number of factors, including higher pretreatment FPG and C-peptide levels, which suggests that the drug is more effective in patients with greater insulin resistance.

4.1.2 Effects of Combined Therapy on Glycaemic Control

Combined Therapy with Oral Agents

North American and European Studies. Troglitazone has been used in combination with other oral drugs in the management of patients with type 2 diabetes mellitus in several clinical trials conducted in North America and Europe.[60,107-109]

Among these trials, the largest has been a multicentre double-blind study of 552 patients randomised to 7 treatment groups for 1 year: glibenclamide 12 mg/day, troglitazone 200, 400 or 600 mg/day, or combined therapy with glibenclamide 12 mg/day plus troglitazone 200, 400 or 600 mg/day.[109] Results for the 545 patients evaluable for efficacy indicate significantly better glycaemic control with combined therapy than with glibenclamide or troglitazone monotherapy. At the end of the treatment period, mean FSG levels with combined therapy were 3.0 to 4.4 mmol/L lower than those with glibenclamide monotherapy ($p \leq 0.0001$), while FSG levels with troglitazone monotherapy were similar to those achieved with glibenclamide monotherapy (+1.1 to –0.6 mmol/L; not significant). HbA_{1c} values with combined treatment were 1.6 to 2.7% lower (absolute difference) than those with glibenclamide monotherapy ($p \leq 0.0001$), whereas HbA_{1c} values with troglitazone monotherapy were generally similar to those achieved with glibenclamide monotherapy [+1.0% ($p \leq 0.001$) to –0.1% (not significant)]. In terms of meeting clinical practice guidelines, approximately 40% of patients treated with troglitazone 600 mg/day plus glibenclamide achieved the optimal American Diabetes Association (ADA) target of $HbA_{1c} \leq 7\%$, and 60% achieved an $HbA_{1c} \leq 8\%$

Table III. Large (n > 100) trials conducted in North America and Europe comparing troglitazone (T) with other oral agents as monotherapy in patients with type 2 diabetes mellitus

Reference	Study design [duration; wk]	Dosage regimen (mg) [no. of patients evaluated]	Mean effect on FSG (% change *vs* baseline or comparator)	Mean effect on HbA_{1c} (% relative change *vs* baseline or comparator)	Mean effect on serum insulin levels (% change *vs* baseline or comparator)
Claudi et al.[84]a	mc, db, r [26][b]	T 100 od [786][c]	1.11** (ratio[d])	NA	0.77 (ratio[d])
		T 200 od	1.08* (ratio[d])	NA	0.72 (ratio[d])
		T 600 od	0.97 (ratio[d])	NA	0.68 (ratio[d])
		G titrated to response			
Ghazzi et al.[85]	mc, nb, r [48]	T 800 od [114][c]	↓17.3 *vs* baseline**	↓5.6 *vs* baseline	↓26.4 *vs* baseline*
		G titrated to response	↓19.4 *vs* baseline**	↓2.2 *vs* baseline	↑21.9 *vs* baseline
Serrano-Rios et al.[89]a	mc, r [26]	T 100 od [372][c]	↑14.4 *vs* M**	↑8.2 *vs* M*	↓15.3 *vs* M*
		T 200 od	↑11.1 *vs* M*	↑8.2 *vs* M*	↓20.0 *vs* M**
		T 600 od	↑2.2 *vs* M	No difference *vs* M	↓23.5 *vs* M**
		M titrated to response			

a Study published as an abstract.

b 52-week study; interim results reported at 26 weeks.

c Total number of patients in study.

d Results expressed as a ratio, levels with T to levels with G at end of study.

db = double-blind; **FSG** = fasting serum glucose; **G** = glibenclamide (glyburide); **HbA_{1c}** = glycosylated haemoglobin; **M** = metformin; **mc** = multicentre; **NA** = data not available; **nb** = nonblind; **od** = once daily; **r** = randomised; ↑ = increased; ↓ = decreased; * $p < 0.05$, ** $p < 0.001$ *vs* G or M.

(the level above which action to lower blood glucose is advised). The proportion of patients who achieved these HbA_{1c} targets was somewhat lower among those receiving the lower troglitazone dosages in combination with glibenclamide (≈22% of patients achieved HbA_{1c} ≤7%, and ≈33% of patients achieved HbA_{1c} ≤8%).

Preliminary results[107] of an open-label extension of the study, in which 43 patients completed 116 weeks of treatment with troglitazone 600 mg/day plus glibenclamide 12 mg/day, indicate that glycaemic control was maintained with combined therapy over this period (fig. 5).

The effects of combined therapy with troglitazone 400mg once daily plus metformin 1000mg twice daily were evaluated by Inzucchi et al.[60] in an analysis of 28 patients who first received treatment for 3 months with either of these agents as monotherapy in a randomised fashion. Both troglitazone and metformin monotherapy reduced FPG levels by 20% from baseline [from 15.3 to 12.3 mmol/L with troglitazone ($p = 0.01$); from 15.9 to 12.7 mmol/L with metformin ($p < 0.001$)] and postprandial glucose levels by 25% from baseline ($p < 0.001$ for both treatment groups *vs* baseline). Patients then received combined therapy for a further 3 months, which resulted in an additional 18% (2.3 mmol/L) decline in FPG levels ($p = 0.001$) and an additional 21% (3.0 mmol/L) reduction in postprandial glucose levels ($p < 0.001$). During the 3-month period of combination therapy, an absolute reduction of 1.2% ($p < 0.001$) in HbA_{1c} was achieved.

Japanese Studies. The clinical efficacy of troglitazone in combination with sulphonylurea drugs was also demonstrated in various studies conducted in Japan,[83,94,110-112] including a double-blind multicentre trial of 248 patients with type 2 diabetes mellitus who had poor glycaemic control despite dietary interventions and sulphonylurea therapy.[111] Patients were randomised to receive, in addition to their current sulphonylurea treatment regimen, troglitazone 200mg twice daily or placebo for 12 weeks. Among patients randomised to troglitazone therapy, FPG levels declined significantly from 10.8 mmol/L at baseline to 9.1 mmol/L at the end of the treatment period ($p < 0.001$), whereas a nonsignificant change from 10.5 to 10.7 mmol/L was observed among placebo recipients. Similar modifications were noted with respect to fasting C-peptide levels and HbA_{1c} values: C-peptide levels were reduced by approximately 18% from baseline ($p = 0.002$) with troglitazone but were essentially unchanged with placebo, and troglitazone reduced HbA_{1c} from 9.2 to 8.5% ($p < 0.001$), while placebo had no significant effect on this parameter (9.0% at baseline *vs* 9.2% at the end of treatment). In this study and in another large trial without a placebo control group in which patients received a sulphonylurea plus troglitazone 400 to 800 mg/day for 16 weeks,[110] approximately 40 to 50% of troglitazone recipients demonstrated a reduction in FPG levels of at least 20% from baseline.

The long term effects of troglitazone on glycaemic control, when used in combined therapy, have been shown in a Japanese study of 137 patients treated for 1 year with a sulphonylurea agent plus

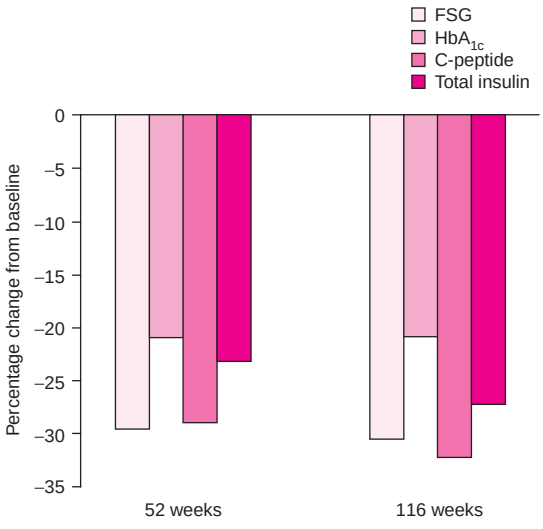

Fig. 5. Long term changes in glycaemic parameters among 43 patients with type 2 diabetes mellitus receiving combined therapy with troglitazone 600 mg/day plus glibenclamide 12 mg/day for 116 weeks.[107] Results of an open-label extension of a double-blind trial; $p < 0.05$ *vs* baseline for all reductions. **FSG** = fasting serum glucose; **HbA_{1c}** = glycosylated haemoglobin.

troglitazone 200 to 800 mg/day.[94] FPG was reduced by 22% over the period from baseline to 16 weeks (10.6 *vs* 8.3 mmol/L; $p < 0.001$), and FPG levels remained between 8.4 and 9.1 mmol/L until the end of the 1-year treatment period. HbA_{1c} values were reduced from 9.1% at baseline to 7.7% at week 16 ($p < 0.001$), and ranged from 7.7 to 8.2% until the end of treatment. (The long term efficacy of combined therapy with troglitazone plus glibenclamide was also demonstrated in a recent North American trial.[107])

In a 6-month study of 49 Japanese patients receiving combined therapy, which included troglitazone 200 to 400 mg/day, older patients (≥60 years) who responded well to therapy tended to require lower troglitazone dosages than younger patients (<60 years).[83]

Combined Therapy with Insulin

North American and European Studies. Results of 2 large multicentre studies showed that, when given in combination with insulin, troglitazone improves glycaemic control in patients with type 2 diabetes mellitus.[113,114] All patients had poor glycaemic control and were receiving at least 30 U/day of insulin.

In the study by Schwartz and colleagues,[113] a total of 350 patients were randomised to receive concomitant treatment with troglitazone 200 mg/day (n = 116), troglitazone 600 mg/day (n = 116) or placebo (n = 118) for 26 weeks. The study protocol did not allow the insulin dosage to be increased; however, the insulin dosage could be reduced during the trial if necessary to avoid hypoglycaemia. Intention-to-treat analysis showed that FSG levels were reduced by 16.4% from baseline with troglitazone 200 mg/day (11.9 to 10.0 mmol/L) and by 23% with troglitazone 600 mg/day (11.9 to 9.2 mmol/L), and insulin dosage was reduced by 11 and 29%, respectively. In contrast, FSG levels were essentially unchanged, as was insulin dosage, among placebo recipients ($p < 0.001$ for all comparisons of troglitazone *vs* placebo). Absolute reductions from baseline in HbA_{1c} values were 0.8 and 1.4%, respectively, for troglitazone 200 and 600 mg/day, which translated into relative reductions of approximately 8 and 15%. These changes were significant versus placebo ($p < 0.001$).

An extension of this study was conducted, in which 286 patients were treated with troglitazone 200, 400 or 600 mg/day for a further 13 to 17 months (total duration up to 23 months).[115] Patients initially on placebo received troglitazone 400 mg/day in the extended study. Preliminary results showed that troglitazone in combination with insulin maintained improvements in glycaemic control during long term administration. Insulin dosages also remained lower compared with baseline throughout the extended study period; at the end of the extended study, mean insulin dosages were 58, 59 and 44 U/day among patients receiving troglitazone 200, 400 and 600 mg/day, respectively, compared with baseline insulin dosages of 71 to 75 U/day ($p < 0.01$ for all comparisons).

The second large trial was conducted by Buse et al.[114] and comprised a 26-week double-blind study of 222 insulin-treated patients with type 2 diabetes mellitus who received concomitant therapy with troglitazone 200 or 400mg once daily or placebo, as well as a 48-week open-label extension involving 173 of the patients. The primary dual end-point of the trial was (i) at least a 50% reduction in daily insulin dosage and (ii) either a decrease in FSG of >15% or an FSG level of <7.8 mmol/L. This was achieved by significantly more patients treated with troglitazone 200 or 400 mg/day than placebo (22, 27 and 7% of patients, respectively, $p < 0.01$). Significant changes in metabolic parameters were not expected in the double-blind phase because the protocol required a 25% reduction in insulin dosage in response to a 5% decline in FSG. Nevertheless, small but significant reductions in FSG and HbA_{1c} were noted with troglitazone compared with placebo. During the open-label phase, when all patients were started on troglitazone 200 mg/day (titrated to 400 mg/day in most patients) and adjustments in insulin dosage were made at the discretion of the individual investigators, reductions in FSG and HbA_{1c} were more

marked than in the double-blind phase and insulin dosage reductions were also achieved.

Japanese Studies. A randomised double-blind placebo-controlled study of 190 patients with diabetes mellitus (>75% of patients had type 2 diabetes mellitus) demonstrated that addition of troglitazone 200mg twice daily to an existing insulin regimen significantly improved glycaemic control.[116] Mean HbA_{1c} values declined from approximately 10% at baseline to 9.3% after 16 weeks of combined therapy ($p < 0.001$), whereas patients receiving insulin plus placebo had no significant change in HbA_{1c} values. Troglitazone therapy was also associated with a slightly greater reduction in insulin dosage than placebo (0.51 *vs* 0.20 U/day reduction; $p < 0.05$). In a smaller trial of 17 patients, addition of troglitazone 400 mg/day to conventional insulin therapy for 12 weeks reduced FPG levels by 23% and HbA_{1c} values by 8% (relative reduction) from baseline.[117] In general, troglitazone tended to have a greater effect in patients receiving higher insulin dosages than among those receiving lower insulin dosages.

4.1.3 Effects on Lipid Metabolism

The effects of troglitazone on lipid metabolism in clinical trials of patients with type 2 diabetes mellitus receiving monotherapy or combined therapy have generally been variable and minor, with the notable exception of consistent reductions in fasting serum triglyceride levels of 13 to 26%.[28-31,65,81,82] In clinical trials of monotherapy or combined therapy, troglitazone increased serum levels of LDL-cholesterol by as much as 13% from baseline, HDL-cholesterol by up to 16% and total cholesterol by up to 5%, but the ratio of total cholesterol to HDL-cholesterol and the ratio of LDL- to HDL-cholesterol did not significantly change.[65]

4.2 Therapeutic Potential in Patients with Impaired Glucose Tolerance

IGT affects approximately 11% of the US population and is a major risk factor for diabetes mellitus. In addition, hypertension, atherosclerosis, angina and other cardiovascular problems are more prevalent in individuals with IGT than in those with normal glucose tolerance.[118] Patients with IGT progress to overt type 2 diabetes mellitus at a rate of about 1 to 5% per year,[118] although rates of progression are higher in certain subpopulations, such as women with a history of gestational diabetes[119] and Japanese patients.[120]

Nolan and colleagues[63] evaluated the effects of troglitazone 200mg twice daily for 12 weeks in a double-blind randomised placebo-controlled study of 18 nondiabetic obese individuals, 9 of whom had IGT as defined by World Health Organization (WHO) criteria. A modest but statistically significant 4% reduction in mean FPG levels, from 5.5 mmol/L at baseline to 5.3 mmol/L at 12 weeks ($p = 0.02$), was achieved with troglitazone; FPG levels were unchanged from baseline (5.4 mmol/L) among placebo recipients. Troglitazone had a more marked effect on mean fasting plasma insulin levels, which were reduced from 18 to 10 mU/L ($p = 0.002$) compared with a nonsignificant reduction from 22 to 20 mU/L with placebo. Blood pressure (BP) was reduced from 130/81 to 125/77mm Hg ($p \leq 0.05$) with troglitazone, but was increased moderately with placebo from 123/78 to 129/79mm Hg ($p = 0.001$ for systolic BP). Small statistically insignificant changes were noted in both groups with respect to serum lipid levels.

The study also included oral glucose tolerance tests (OGTT) and meal tolerance tests (MTT), as well as intravenous glucose tolerance tests (IGTT) and hyperinsulinaemic euglycaemic clamp studies to evaluate insulin sensitivity and glucose disposal rates. Troglitazone was associated with 25 and 24% reductions in the incremental area under the curve (AUC) for glucose in the OGTT and MTT, respectively, and corresponding reductions in incremental AUC for insulin were 40 and 41%. In contrast, placebo had essentially no effect on these parameters. Troglitazone was also associated with significantly increased glucose disposal and improved insulin sensitivity.

In a similar multicentre study of 46 nondiabetic individuals with IGT who were randomised to receive troglitazone 400mg once daily or placebo for 12 weeks, troglitazone significantly improved glu-

cose tolerance compared with placebo.[121] During OGTT, incremental AUC values for glucose, insulin and C-peptide were significantly reduced by troglitazone, and at the end of the study period 80% of troglitazone recipients had converted to normal glucose tolerance compared with 48% of placebo recipients ($p = 0.016$). Although troglitazone was not associated with a reduction in fasting serum levels of glucose or insulin, this may have been because these values were in the normal range before treatment. Serum triglyceride levels were reduced by approximately 18% among troglitazone recipients compared with no change among placebo recipients ($p < 0.01$). Other serum lipid levels and BP measurements were not significantly affected in either group.

Another 12-week randomised double-blind study compared troglitazone 200 and 400mg once daily and placebo in a group of 37 Hispanic women with IGT and a history of gestational diabetes (a very high-risk group for developing type 2 diabetes mellitus).[122] Although troglitazone did not affect glucose tolerance, it improved insulin sensitivity and lowered circulating insulin levels.

5. Tolerability

5.1 Overall Tolerability Profile

In clinical trials, the type and incidence of adverse events associated with troglitazone were broadly similar to those observed with placebo. Tolerability data from the manufacturer derived from North American clinical trials of patients with type 2 diabetes mellitus and involving a total of 1450 troglitazone-treated patients and 492 placebo recipients are presented in figure 6.[65] The most frequently reported adverse events with both troglitazone and placebo were infection (18 *vs* 22%), headache (11 *vs* 11%) and pain (10 *vs* 14%). Other adverse events reported in 5 to 8% of troglitazone recipients and 4 to 7% of placebo recipients included accidental injury, asthenia, dizziness, back pain (presumably excluded from 'pain' category), nausea, rhinitis, diarrhoea, urinary tract infection (presumably excluded from 'infection' category), peripheral oedema and pharyngitis. The rate of treatment withdrawal during clinical trials was approximately 4% for both troglitazone and placebo.[65]

Clinical trials of troglitazone monotherapy conducted in Europe and North America, the methods of which are summarised in table II, also showed that the nature and incidence of adverse events were similar between troglitazone and placebo. In these studies the most frequently reported adverse events were gastrointestinal problems, such as diarrhoea and nausea, as well as headache, asthenia, fatigue and malaise. No clear dose relationship was noted with respect to the adverse events of troglitazone in these studies, which included a dosage range of 10 to 800 mg/day. Tolerability data from similar clinical studies of troglitazone monotherapy conducted in Japan (section 4.1.1) were not markedly different from those of North American and European studies.

As would be expected from the mechanism of action of troglitazone (section 2.1), patients receiving the drug as monotherapy are not at risk of developing hypoglycaemia; however, patients receiving concomitant treatment with insulin may develop hypoglycaemia necessitating a reduction in insulin dosage.[65] Aside from this, adverse events observed when troglitazone was co-administered with insulin were similar to those seen during troglitazone monotherapy.

Tolerability data from studies in which troglitazone was administered concomitantly with other oral antidiabetic agents (section 4.1.2) are limited. Results of a randomised multicentre 1-year trial of 552 patients with type 2 diabetes mellitus indicated similar rates of adverse events and withdrawals due to adverse events among patients receiving glibenclamide, or troglitazone 200, 400 or 600 mg/day, alone or in combination with glibenclamide 12 mg/day.[109] Hypoglycaemia has been reported in some studies in which troglitazone was used in combination with a sulphonylurea agent.[94,111]

In clinical trials, troglitazone was more likely than placebo to produce small reductions in neutrophil counts (within the normal range), haemoglobin

(below the normal range for 5% of troglitazone and 4% of placebo recipients) and haematocrit.[65] These haematological effects may be the result of a dilution effect related to plasma volume expansion with troglitazone, as a study of 24 healthy volunteers showed that troglitazone increased plasma volume by 6 to 8% compared with placebo. Although no increase in the incidence of adverse events potentially associated with expanded plasma volume (e.g. congestive heart failure) has been demonstrated with troglitazone in clinical trials, peripheral oedema occasionally develops among troglitazone recipients and the drug is not recommended in patients with New York Heart Association (NYHA) class III or IV congestive heart failure.[65]

Importantly, troglitazone does not appear to induce left ventricular hypertrophy in patients with type 2 diabetes mellitus. Left ventricular mass index (measured by pulsed Doppler and 2-dimensional echocardiography) did not change from baseline after 48 weeks of treatment with troglitazone 800 mg/day.[85] A 48-week extension of this trial found no evidence of cardiac enlargement among patients with type 2 diabetes mellitus treated with troglitazone for a total of 96 weeks.[123] This is in contrast to earlier studies in rodents in which heart enlargement without microscopic changes was observed at exposures exceeding 7 times the AUC produced by a 400mg dose in humans.[65]

Many of the studies discussed in section 4.1 monitored patients for BP, heart rate and electrocardiographic changes. Troglitazone was not associated with clinically significant modifications in these parameters. Although a few studies demonstrated small but statistically significant increases in bodyweight with troglitazone therapy (an effect also shown in rodent models[58]), these changes were of minor clinical significance, and the majority of studies in which bodyweight was monitored showed no change with troglitazone therapy.

5.2 Liver Dysfunction

Following several reports of liver damage in patients taking the drug, troglitazone was voluntarily withdrawn (or at least temporarily suspended) from the UK market in late-1997 by the manufacturer in that country but remained available in the US and Japan.[124,125] Reversible elevations in alanine aminotransferase (ALT) levels >3 times the upper limit of normal were documented in 1.9% of troglitazone recipients compared with 0.6% of placebo re-

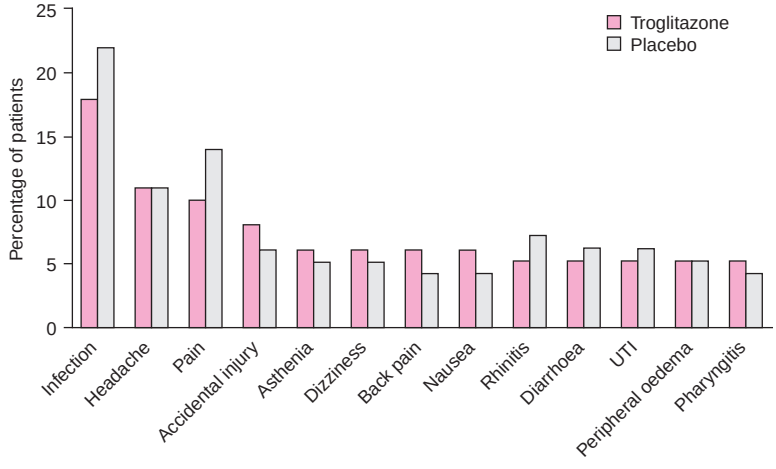

Fig. 6. Adverse events reported in ≥5% of patients with type 2 diabetes mellitus in placebo-controlled North American trials of troglitazone.[65] Combined data from 1450 troglitazone and 492 placebo recipients. **UTI** = urinary tract infection (presumably excluded from 'Infection' category).

cipients in controlled clinical trials conducted in North America.[65]

Since its market launch, troglitazone has been associated with a number of reports of idiosyncratic liver dysfunction which, in a small number of cases, has led to death or the need for liver transplantation.[126-132] Thus, although approximately 2% of patients receiving troglitazone can be expected to discontinue therapy because of elevated liver enzymes, in only very rare cases has permanent liver damage developed despite discontinuing the drug.[126]

The manufacturer has introduced a series of labelling changes for troglitazone,[126,127,129,130,133,134] recommending close monitoring of liver enzyme levels and for clinical signs of liver dysfunction (see section 7). There is disagreement as to the exact number of 'validated' deaths associated with troglitazone in the US; however, the US manufacturer states that there have been 26 reports of liver-related deaths and 4 separate reports of liver transplant in the US as of 30 November 1998 (0.0022% of >1.4 million troglitazone-treated patients).[126] This translates into an incidence of liver-related death or transplant in patients receiving troglitazone of approximately 1 case in 50 000 patients, which is roughly in agreement with an estimate of 1 case in 60 000 troglitazone-treated patients in the US as of July 1998.[134] Focusing specifically on liver-related deaths, the risk associated with troglitazone therapy appears to have steadily declined from 1 in 44 000 prior to the inclusion of liver enzyme monitoring in the product labelling (March to October 1997), to 1 in 65 000 during the period from 1 November 1997 to 30 November 1998, and to approximately 1 in 100 000 among patients beginning therapy in 1998, i.e. after the incorporation of a boxed warning and increased monitoring requirements in the product labelling.[126] Most of these serious events occurred in patients with complex medical histories, including potentially confounding concomitant medical conditions or medications that have been associated with liver dysfunction.[126] In view of the rare occurrence of this serious problem, the FDA in the US maintains that the benefits of troglitazone outweigh its risks in patients with type 2 diabetes mellitus.[130,135] However, the FDA will continue to closely monitor the rate of liver dysfunction in patients treated with troglitazone.[135]

A recently published evaluation of 35 cases of liver dysfunction in Japan indicated that elevation of liver enzymes typically occurred within 2 to 5 months of starting troglitazone therapy.[131] Upon discontinuation of the drug, liver enzyme levels generally declined rapidly, usually to less than half of the peak level within 4 weeks. The peak and recovery of total bilirubin levels was delayed compared with that of ALT levels. At the time of discontinuation of troglitazone, total bilirubin levels were less than 5 mg/dl (85.5 μmol/L) in the 31 patients who recovered, but were greater than 8 mg/dl (136.8 μmol/L) in the 4 patients who subsequently died from liver failure, thus suggesting a possible prognostic indicator.

6. Drug Interactions

Although troglitazone is not metabolised by the cytochrome P450 (CYP) 3A isoenzyme pathway,[136,137] it appears to induce drug metabolism by CYP3A4.[65] Indeed, troglitazone has been shown to decrease plasma concentrations of terfenadine by 50 to 70%,[65] cyclosporin by 30%[136,138] (with precipitous reductions in some case reports[139,140]), and both ethinylestradiol and norethindrone by 30% (potentially leading to loss of contraceptive efficacy)[65] when administered concomitantly with each of these CYP3A4 substrates. These findings should also be considered when troglitazone is prescribed concomitantly with other CYP3A4 substrates, such as tacrolimus and some HMG-CoA reductase inhibitors.[65]

As mentioned in section 3, troglitazone is highly bound to plasma protein. However, displacement interactions between troglitazone and other drugs with high plasma protein binding, such as warfarin and glibenclamide, do not appear to occur.[65,141] Nevertheless, despite the lack of a pharmacokinetic interaction between troglitazone and glibenclamide in patients with type 2 diabetes mellitus,[141] the

combination of troglitazone and sulphonylureas may further decrease FPG levels via the respective pharmacodynamic effects of these drugs.[65] It is also noteworthy that the addition of troglitazone to warfarin therapy significantly increased prothrombin time and necessitated a reduction in warfarin dosage in a single case report of a 51-year-old man receiving multiple drug therapy.[142]

Troglitazone-treated patients with type 2 diabetes mellitus who received a single administration of a moderate amount of alcohol (ethanol 0.6 mg/kg; ≈4 glasses of wine) did not have an increased risk of acute hypoglycaemia in a placebo-controlled study.[143] FSG, 4-hour postprandial serum glucose levels and other parameters of glycaemic control were not affected by concomitant alcohol administration.

Concomitant administration of cholestyramine and troglitazone is not recommended, since this reduces the absorption of troglitazone by approximately 70%, as demonstrated by marked reductions in AUC values for troglitazone and its main metabolites.[144]

Concurrent administration of paracetamol (acetaminophen) and troglitazone does not alter the pharmacokinetics of either agent.[65,145] Similarly, concomitant repeated administration of troglitazone did not affect the steady state pharmacokinetics of digoxin in healthy volunteers (modifications to troglitazone pharmacokinetic parameters were not assessed in this analysis).[137] However, urinary excretion of 6-β-hydroxycortisol and the ratio of 24-hour urinary 6-β-hydroxycortisol to cortisol excretion was significantly increased in these volunteers,[146] results which are consistent with other known inducers of CYP3A, such as rifampicin and phenytoin.[147,148]

7. Dosage and Administration

Troglitazone is orally administered and is indicated as monotherapy or for use in combination with other oral agents or insulin for the treatment of patients with type 2 diabetes mellitus. Troglitazone should be taken with a meal since this enhances absorption of the drug. The recommended dosage regimen of troglitazone in the US is 200 to 600mg once daily, although the usual dosage is 400mg once daily. If there is no response to the maximum dosage after 1 month, the drug should be discontinued in favour of alternative therapy. In Japan, the recommended dosage regimen of troglitazone is 200mg twice daily (after meals in the morning and evening).

When troglitazone is added to insulin therapy, it should be initiated at a dosage of 200mg once daily and the current insulin dosage should be continued. The dosage of troglitazone may be increased after 2 to 4 weeks for patients not responding adequately to this combined therapy. Insulin dosage may need to be reduced by 10 to 25% if FPG levels decrease to <6.7 mmol/L in patients receiving concomitant treatment with insulin and troglitazone, and further adjustments should be made on the basis of glucose-lowering response.

Dosage adjustment of troglitazone in patients with renal insufficiency is not necessary because almost none of the drug is eliminated unchanged in the urine. Troglitazone is not recommended in patients with hepatic impairment.

Rare cases of liver dysfunction have been reported with troglitazone (section 5.2), and close monitoring of liver enzyme levels is therefore necessary. The recommended timetable for liver enzyme monitoring, which involves at least 11 tests during the first year of therapy, is as follows: at the start of therapy, monthly for the first 8 months of treatment, every 2 months for the remainder of the first year, and periodically thereafter. Patients whose ALT levels rise moderately to >1.5 to 2 times the upper limit of normal during troglitazone therapy should have ALT levels repeated within a week and then weekly until they either return to normal or reach 3 times the upper limit of normal, in which case the drug should be discontinued. Troglitazone therapy should not be initiated in patients with ALT levels ≥1.5 times the upper limit of normal.

8. Place of Troglitazone in the Management of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a common disease associated with a number of serious chronic complications[13] and significant costs.[149,150] It is characterised by insulin resistance, impaired pancreatic β cell function and increased hepatic glucose production. Troglitazone is the first of a new class of oral antidiabetic drugs, the thiazolidinediones, which work by enhancing the effects of insulin at peripheral target sites. Thus, troglitazone markedly increases glucose disposal by skeletal muscle and adipose tissue and appears to modestly reduce hepatic glucose production. The mechanism of action of troglitazone is dependent on the presence of insulin and does not involve direct stimulation of pancreatic β cells to release insulin. Patients receiving troglitazone as monotherapy are therefore not at risk of developing hypoglycaemia.

Dietary management underpins the treatment of type 2 diabetes mellitus, but nearly all patients eventually require drug therapy in order to achieve and maintain adequate glycaemic control. For many years, the mainstay of pharmacotherapy in patients with type 2 diabetes mellitus has been sulphonylurea agents such as glibenclamide. These drugs act primarily by stimulating secretion of insulin by the pancreatic β cells and can therefore cause hypoglycaemia.[151,152] Hypoglycaemic episodes associated with sulphonylureas, although distressing, are usually self-managed, but a minority of events are associated with significant direct medical costs and lost productivity.[153]

Other oral treatment options in patients with type 2 diabetes mellitus include the biguanide metformin and the α-glucosidase inhibitor acarbose, both of which are associated with abdominal discomfort and other gastrointestinal adverse events, but neither of which causes hypoglycaemia.[151,154] Metformin, which causes a marked reduction in hepatic glucose production and a modest increase in glucose uptake, has been associated with lactic acidosis, although this is a rare adverse event and occurs primarily in patients with renal impairment.[151,154] Acarbose works by delaying absorption of glucose from the gastrointestinal tract, has only a modest effect on improving glycaemic control and has not made a major impact on the management of type 2 diabetes mellitus to date.[152] Unfortunately, because of the progressive nature of the disease, a large proportion of patients with type 2 diabetes mellitus eventually develop secondary treatment failure with oral antidiabetic agents and require combined therapy and/or insulin treatment.

In the US, troglitazone was initially approved for use only as adjunctive therapy in patients with type 2 diabetes mellitus whose hyperglycaemia was inadequately controlled (HbA_{1c} >8.5%) despite insulin therapy of >30 U/day. Subsequently, the FDA approved its use as monotherapy and in combination with sulphonylureas in patients with type 2 diabetes mellitus.[155]

Clinical trials conducted in North America, Europe and Japan consistently demonstrated the efficacy of troglitazone in improving glycaemic control in patients with type 2 diabetes mellitus. In virtually all trials in which troglitazone was administered as monotherapy or in combination with either oral antidiabetic agents (e.g. sulphonylureas) or insulin, statistically and clinically significant reductions in FSG levels and HbA_{1c} values were achieved. Fasting serum insulin and triglyceride levels (i.e. additional cardiovascular risk factors) were also typically reduced. Comparative studies with either glibenclamide or metformin indicated similar glycaemic control between troglitazone and these agents. Serum insulin levels were lower with troglitazone than with glibenclamide. Clinical trials of approximately 2 years' duration indicate that glycaemic control is maintained with troglitazone on a long term basis in patients with type 2 diabetes mellitus. Although on the basis of data for other antidiabetic agents (e.g. results from the UKPDS), it can be predicted that good glycaemic control with troglitazone will reduce the risk of long term diabetic complications, there are as yet no hard data to confirm this.

Studies of troglitazone in patients with IGT conducted to date have been relatively short (12

weeks) and therefore have been unable to evaluate whether the drug prevents progression from IGT to frank type 2 diabetes mellitus. Thus, although troglitazone was able to normalise glucose tolerance in patients with IGT, long term trials of adequate size will be needed to determine whether troglitazone can maintain this effect and ultimately delay or prevent progression to overt diabetes mellitus (an effect demonstrated several years ago with tolbutamide[156]). However, as pointed out by Yoshioka and others,[157,158] weight reduction by appropriate dietary management is an important first step for improving IGT in obese individuals before starting pharmacotherapy. It is also noteworthy that the US National Institutes of Health (NIH) discontinued the troglitazone treatment arm of the Diabetes Prevention Program (DPP) study (investigating whether clinical interventions can prevent or delay the development of type 2 diabetes mellitus in patients at risk), after a patient developed liver failure and died. The patient was found to have other serious complications (e.g. extensive necrosis in the bowel) which may have contributed to the cause of death, but the NIH acted cautiously because it was unwilling to accept any risk of serious adverse events in the generally healthy patient population of the DPP study, particularly since the benefits of troglitazone therapy in this patient group have not yet been clearly demonstrated. On the other hand, the US manufacturer of troglitazone has pointed out that the NIH decision has no bearing on the safety of troglitazone in its approved indication, the treatment of patients with type 2 diabetes mellitus.[159]

In general, troglitazone is well tolerated by the majority of patients with type 2 diabetes mellitus. However, discontinuation of troglitazone because of elevated liver enzyme levels is necessary in approximately 2% of patients receiving the drug. A number of postmarketing reports of liver dysfunction prompted a series of labelling changes for troglitazone, recommending close monitoring of liver enzyme levels and for clinical signs of liver dysfunction. The overall incidence of permanent liver damage leading to death or liver transplantation has been estimated to be approximately 1 case in every 50 000 to 60 000 patients treated with troglitazone in the US. However, the labelling changes appear to have reduced the risk of permanent liver damage: recent estimates focusing specifically on the risk of liver-related death among patients who started troglitazone therapy in the US in 1998 indicate a risk of approximately 1 in 100 000. In view of the rare occurrence of this serious problem, the FDA in the US maintains that the benefits of troglitazone outweigh its risks in patients with type 2 diabetes mellitus, although they will continue to closely monitor the rate of liver dysfunction in patients treated with troglitazone.

Like most new drugs, the acquisition cost of troglitazone is high relative to older, more established agents, such as the sulphonylureas. This factor, along with the cost of liver enzyme monitoring and the potential for adverse events, must be weighed against the potential benefits of the drug.

In summary, troglitazone enhances the effects of insulin at peripheral target sites, thus affecting a common underlying characteristic of type 2 diabetes mellitus – insulin resistance. Troglitazone improves glycaemic control in patients with type 2 diabetes mellitus when used as monotherapy or in combination with other oral antidiabetic drugs or insulin, and its overall efficacy in glycaemic control is similar to that of sulphonylureas or metformin. Although troglitazone is generally well tolerated, frequent monitoring of liver enzyme levels (e.g. at least 11 tests during the first year of therapy) is required to reduce the risk of the rare occurrence of serious hepatic dysfunction. Drug acquisition and liver function monitoring costs, as well as potential adverse effects, are important factors that may ultimately determine the precise place of troglitazone in the management of type 2 diabetes mellitus. Nevertheless, as the first member of a new class of oral antidiabetic agents, the thiazolidinediones, troglitazone offers an effective treatment option in patients with type 2 diabetes mellitus through its action of improving insulin sensitivity.

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