Troglitazone: a review of its use in the management of type 2 diabetes mellitus

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Authors' objectives
To review the use of troglitazone in the management of type 2 diabetes mellitus. The review included epidemiological, pharmacological and tolerability data in addition to effectiveness data.

Searching
AdisBase (Database of Adis International, New Zealand), MEDLINE and EMBASE were searched up until Feb 1999 for literature published in any language since 1966. AdisBase search terms included: 'toglitazone', 'CI-991', 'CS-045', 'GR-92132' and 'GR-92132'. In addition MEDLINE and EMBASE search terms included '97322-887-7'. The bibliographies of retrieved articles were searched and the drug company developing the drug were contacted for additional data.

Study selection
Study design was not used as an inclusion criterion but large, well-controlled trials with appropriate methodology (not stated) were preferred. Studies reported in the review included double-blinded and non-blinded randomised controlled trials (RCTs) of 12-116 weeks duration (most were 12-48 weeks).

Specific interventions included in the review
Troglitazone (10mg-800mg/day) used as a monotherapy or in combination with other oral antidiabetic drugs (glibenclamide, metformin, and sulphonylurea) or insulin. Comparators included other oral antidiabetic drugs and placebo groups.

Participants included in the review
Patients with type 2 diabetes mellitus or impaired glucose tolerance. Impaired glucose tolerance was typically defined as fasting plasma or serum glucose (FPG or FSG) levels between 7 and 15mmol/L (126 and 270mg/dl). Most of the trials reported in the review involved patients (aged 40-75yrs) with type 2 diabetes mellitus that was inadequately controlled by diet alone (or by diet and sulphonylurea, but sulphonylurea was continued during a washout period). Combination therapy with troglitazone usually involved patients with inadequate glycaemic control despite dietary and pharmacological treatment. Patients with other conditions thought to be associated with insulin resistance, including polycystic ovary syndrome and Werner's syndrome were excluded.

Outcomes assessed in the review
Effects on fasting plasma or serum glucose levels (FPG or FSG), glycosylated haemoglobin levels (HBA), and serum insulin levels. Other outcomes included effects on lipid metabolism (e.g. C-peptide and triglyceride levels) and tolerability as indicated by the nature and number of adverse events.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The number of reviewers involved and the type of data extracted were The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. However, data tables reported in
the review included: bibliographic details, study design, dosage regimen, and effects on FSG, HbA and serum insulin levels.

**Methods of synthesis**

How were the studies combined?

A narrative summary was used with accompanying data tables for larger monotherapy studies with more than 100 participants. The % reduction in the treatment group as compared to placebo was calculated for each of the outcome measures. Where results were reported as mean values at the end of the treatment period, the mean values were adjusted where possible for baseline and investigator centre. Other values at 6 months were estimated using weighted means and some troglitazone doses were estimated from graphical representations of the data.

**How were differences between studies investigated?**

The authors do not state how differences between the studies were investigated.

**Results of the review**

Fifty studies including 2 reviews (the numbers of participants and study designs were not always stated). 36 looked at monotherapy with troglitazone and 14 at combination therapies.

Monotherapy (not clear how many were vs placebo and how many vs other agents; participant numbers not clear for all of the studies):

In large (n>100) trials conducted in North America using troglitazone (200-800mg/day), FSG was reduced by approximately 11 to 33% and HbA by 5-15% compared with placebo or baseline levels. Fasting serum insulin, C-peptide and triglyceride levels were also typically reduced. The effects of troglitazone on glycaemic control were maintained for over 1 year in one trial. In comparative trials of troglitazone monotherapy versus other agents, troglitazone (600 or 800mg/day) had similar efficacy to glibenclamide (titrated to response) in terms of glycaemic control, although only troglitazone was associated with reductions in serum insulin levels. Comparisons between troglitazone and metformin using commonly used dosage regimens also showed similar effects on glycaemic control. Similar effects were seen in studies in Japan as compared to North America and Europe.

Combined therapy (2 troglitazone+ glibenclamide, 1 troglitazone+metformin, 5 troglitazone+sulphonylurea, 5 troglitazone+insulin and one unknown combination study):

Concomitant treatment with troglitazone 220-600mg/day, plus either glibenclamide 12mg/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 (116wks). Other trials of up to 1 year's duration also showed significantly greater reductions in FPG and HbA when troglitazone was added to sulphonylurea in comparison with sulphonylurea monotherapy. The addition of troglitazone (200-600mg/day) to insulin therapy (30 units or more per day) reduced FSG levels, insulin dosage requirements and HbA values, with glycaemic control maintained for up to 23mths in an extension of the largest study (n=286 for the extension study).

**Effects on lipid metabolism (6 studies and 1 review):**

The effects were generally variable and minor for both mono- and combination therapies, with the exception of consistent reductions in fasting serum triglyceride levels of 13-26%.

**Studies in patients with impaired glucose tolerance (3 studies):**

Modest but statistically significant reductions in FPG, mean fasting plasma insulin, blood pressure and serum lipids, and improved glucose tolerance were observed with troglitazone compared to placebo in two of the studies. The remaining study did not show an improvement in glucose tolerance, however, insulin sensitivity and circulating insulin levels were improved.
Tolerability:

In clinical trials, the incidence and type of adverse events associated with troglitazone were broadly similar to those observed with placebo. The most frequently observed adverse effects with both troglitazone and placebo were infection (18 vs 22%), headache (11 vs 11%) and pain (10 vs 14%). The rate of patient withdrawal from studies was approximately 4% for both placebo and troglitazone. Unlike sulphonylurea troglitazone was not associated with hypoglycaemic reactions when administered as a monotherapy.

Authors' conclusions
Troglitazone has been shown to improve glycaemic control in patients with type 2 diabetes mellitus when used as a monotherapy or in combination with other oral antidiabetic drugs or insulin, and its efficacy is similar to that of glibenclamide or metformin.

CRD commentary
This review is based on literature, which attempts to locate both unpublished and published data, without any language restriction. However, the review lacks methodological information and it is not clear how the processes of study selection and data extraction were conducted, including how many individuals were involved. The quality of the studies and the heterogeneity between studies were not assessed before combining them in a narrative summary. Data tables were presented for monotherapy studies but only for those studies with over 100 participants and not studies using combination therapies, which was disappointing. It was also difficult to determine the exact number of studies reported in the review and how many were considered in the overall synthesis and consequently the authors concluding statements. For some studies mentioned in the text there were very few details in terms of study design and participant numbers. In view of these problems the authors' findings should be treated with caution although the recommendations for future research would appear to be valid.

Implications of the review for practice and research
Practice: The authors state that 'troglitazone offers an effective treatment option in patients with type 2 diabetes mellitus'.

Research: The authors state that '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)'

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.