Rapid review

The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review

J Chilcott*
J Wight
M Lloyd Jones
P Tappenden

University of Sheffield School of Health and Related Research, UK

* Corresponding author

Executive summary

Health Technology Assessment 2001; Vol. 5: No. 19

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Background

Type 2 diabetes mellitus is a chronic metabolic disorder that results from defects in insulin secretion and action. The resulting build-up of glucose in the blood can cause a range of diabetic complications, including macrovascular disease (e.g. coronary, cerebral and peripheral vascular disease) and microvascular disease (e.g. retinopathy, nephropathy and neuropathies). People with diabetes are at particularly high risk of cardiovascular disease. This increased risk is related, in part, to hyperglycaemia, and also to hypertension and commonly associated conditions such as adverse lipid profiles.

Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) has shown that maintaining good control of blood glucose reduces the incidence of diabetic complications. It is thought that approximately 1 million people in England and Wales suffer from diabetes, the majority of whom suffer from type 2 diabetes.

Clinical practice guidelines recommend a 'step-up' policy of treatment for type 2 diabetes, starting with diet and lifestyle advice, adding oral blood glucose-lowering agents (principally metformin and the sulphonylureas) and eventually using insulin, if targets are not achieved. Type 2 diabetes tends to be progressive, so therapies may be initially effective but subsequently control is lost. Pioglitazone is one of a new class of oral glucose-lowering drugs, the peroxisome proliferator-activated receptor-gamma agonists, which also include rosiglitazone. These new drugs have a mode of action that differs from that of existing medications.

Objectives

This review was performed to evaluate the use of pioglitazone in its licensed indication, in combination with metformin or sulphonylurea. For completeness, the review also considered its use in combination with insulin and as monotherapy (unlicensed indications).

Methods

A systematic review of the literature, involving a range of databases, was performed to identify all papers relating to pioglitazone, as well as economic or model-based assessments focusing on diabetes mellitus. Full details are described in the main report.

Results

The results of unpublished company-sponsored clinical trials were submitted in confidence to the National Institute for Clinical Excellence (NICE) by Takeda UK Ltd. Information from these studies was included in the version of the report that was sent to the Appraisals Committee, but is not reported here.

Number and quality of studies

Fifteen studies met the inclusion criteria, but full reports were available for only five. Of the 15 studies, nine dealt with pioglitazone alone or in combination with a strict antidiabetic diet. The remainder dealt with pioglitazone in combination with metformin, insulin or a sulphonylurea.

Clinical effectiveness

In both monotherapy and combination therapy, pioglitazone appeared to be effective in reducing blood glucose in patients with poorly controlled type 2 diabetes. However, the US Food and Drug Administration review observed that, when pioglitazone was used as monotherapy, those patients who were changed from another oral antidiabetic agent (metformin or sulphonylurea) to pioglitazone did not achieve the same level of glycaemic control as they had previously experienced. When used in combination with metformin, sulphonylurea or insulin, pioglitazone led to a significant fall in blood glucose and glycosylated haemoglobin (HbA_{1C}) at doses of 15 or 30 mg daily, with a greater effect seen at the higher dose. In addition, both monotherapy and combination therapy studies have demonstrated a fall in triglyceride levels and an increase in high-density lipoprotein cholesterol levels when doses of 30 mg or more of pioglitazone were used.

Pioglitazone treatment is associated with significant weight gain in the short term, which appears to be greater than that seen with other thiazolidinediones. This gain in weight also appears to be greater than that seen in the UKPDS with sulphonylurea or insulin treatment, which in turn was greater than that seen with metformin treatment. This weight gain continues, albeit at a lesser rate, for more than a year. Whether or not weight reaches a plateau after this point cannot be stated with certainty without longer-term follow-up.

There is no direct evidence available on the effect of pioglitazone on diabetic complications, including cardiovascular mortality. However, as the UKPDS study has shown that improved glycaemic control reduces the incidence of microvascular complications, it would be reasonable to expect that this beneficial effect would hold true if a similar improvement in metabolic control was achieved using pioglitazone. Changes in lipid levels could be expected to lead to a reduction in cardiovascular disease risk. However, many studies found that treatment was also associated with significant and progressive weight gain, which would have an adverse effect on the risk of coronary artery disease.

There is also no direct evidence that, for patients whose diabetes is poorly controlled by metformin or sulphonylurea, the addition of pioglitazone is any more effective in improving glycaemic control than moving to a metformin–sulphonylurea combination or starting insulin therapy.

Health economics

Takeda UK Ltd submitted data from a confidential economic model to NICE. Information about this study was included in the version of the report that was sent to the Appraisals Committee, but cannot be reported here.

Conclusions

The evidence suggests that, compared with placebo, pioglitazone is effective in reducing blood glucose in patients with inadequate glycaemic control, both when used as monotherapy and in combination with existing licensed therapies. However, there is no firm evidence to indicate that pioglitazone is more effective than any other antidiabetic agent, particularly when used in combination. Additionally, it is unclear how pioglitazone therapy affects the incidence of microvascular and cardiovascular complications.

Recommendations for research

Evidence is needed regarding:

1. the clinical effectiveness and cost-effectiveness of pioglitazone in combination therapy compared with other possible combination therapies (e.g. rosiglitazone in combination, or sulphonylurea plus metformin, or insulin with or without an oral antidiabetic agent)
2. whether or not the risk of microvascular complications is reduced by the improved glycaemic control achieved using pioglitazone
3. whether or not the risk of cardiovascular events is reduced by the changes in lipid levels achieved using pioglitazone.

Publication

Chilcott J, Wight J, Lloyd Jones M, Tappenden P. The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review. *Health Technol Assess* 2001;5(19).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 00/06/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org ISSN 1366-5278