ABCD position papers: introduction

RH Greenwood, KM Shaw, PH Winocour; on behalf of the Association of British Clinical Diabetologists

The Association of British Clinical Diabetologists (ABCD) is pleased to introduce the publication of the first ABCD Position Paper. The Association plans to produce a series of position statements on clinical topics of practical interest to health care professionals involved in the delivery of diabetes care. Initial papers will address areas already identified by other official bodies such as the National Institute for Clinical Excellence (NICE) – for example, retinopathy screening – and where stated guidelines have proved confusing and often inconsistent with both clinical experience and published evidence.[1] ABCD wishes to produce simplified, practical and pragmatic guidance on issues directly related to implementation of best clinical practice for diabetes.

The first of these papers entitled, 'ABCD position statement on glitazones', has been compiled by lead authors Lyn Higgs (Consultant Diabetologist, Bath) and Andrew Krentz (Consultant Diabetologist, Southampton) following widespread electronic consultation with the ABCD membership. Although this position paper represents a secondary care specialist perspective, we believe that our comments and observations are relevant to colleagues in primary care and to other members of the multidisciplinary diabetes team.

Future papers are planned on the subjects of retinopathy screening, insulin pumps and the management of diabetic ketoacidosis. We hope that these publications, derived from the ABCD consensus, will provide a useful contribution to the provision of high quality diabetes care.

Reference

1. Winocour PH, Shaw KM, Greenwood RH. Will NICE guidelines on the management of type 2 diabetes improve diabetes care? *Pract Diabetes Int* 2004; **21:** 3–6.

ABCD position statement on glitazones

ER Higgs, AJ Krentz; on behalf of the Association of British Clinical Diabetologists

Background

The National Institute for Clinical Excellence (NICE) published new guidance on use of thiazolidinediones (glitazones) in August 2003. This replaced previous guidance on rosiglitazone (Technology Appraisal 9 issued in August 2000) and pioglitazone (Technology Appraisal 21 issued in March 2001). However, this document was followed within days by the extension to the licence of both drugs by the European Agency for the Evaluation of Medicinal products (EMEA) in September 2003.[1]

This paper summarises the views of the Association of British Clinical Diabetologists (ABCD), taking into account additional published evidence about glitazone use and the new European guidelines.

Second-line therapy (4.3)

NICE recommends that the principal use for glitazones is for patients with type 2 diabetes in whom monotherapy with metformin or sulphonylurea has proved inadequate and who are unable to take metformin and sulphonylurea combination therapy because of side effects or contraindications to either of these drugs (4.3.3).

ABCD recommends that the use of glitazones in place of metformin in patients with renal impairment should be considered. Guidelines suggest that metformin should be withdrawn when serum creatinine is elevated,[2] whereas both of the currently available glitazones are licensed in mild to moderate renal failure. However, we would emphasise caution in patients with nephropathy-related fluid retention or left ventricular dysfunction, which may be exacerbated by glitazones – see below. Insulin therapy is often the safest choice in patients with more marked degrees of renal impairment.

The new EMEA licence permits the addition of a glitazone to metformin as the preferred second-line therapy in obese patients. This approach has theoretical advantages as these individuals are often insulin-resistant. Furthermore, glitazones may confer benefits in cardiovascular risk factors (lipids, blood pressure and microalbuminuria). Clinical trials are in progress to determine whether this translates into meaningful reduction in cardiovascular disease. In the meantime, ABCD recommends the option of a glitazone as second-line therapy combined with metformin in the obese patient.

We concur with the change from the previous NICE guidelines on glitazones, i.e. that they should not be used as a substitute for insulin in patients with poor glycaemic control on maximum tolerated doses of sulphonylurea plus metformin. Substitution of either the sulphonylurea or metformin with a glitazone in this situation often leads to a deterioration in glycaemic control and should be discouraged.

Monotherapy (3.3)

The NICE guidelines were published just six days before the EMEA announced licence changes for gli-

tazones. These drugs are effective as monotherapy[3,4] and are now approved for monotherapy if metformin is contraindicated or not tolerated. This may be particularly appropriate in obese patients. It is unfortunate that the NICE guidelines became almost instantaneously out of phase with the product licences for both glitazones. NICE may choose to reconsider this indication before the next scheduled review in 2006, although as yet there has been no clear expression of intent.

Triple therapy (4.3.6)

The 2003 NICE guideline acknowledges that so-called triple therapy with a sulphonylurea, metformin and a glitazone is widely practised in the UK, but does not offer clear guidance. There is evidence that this is safe, and can significantly improve glycaemic control.[5,6] South Asian patients, who have a greater tendency to insulin resistance than white patients, may be particularly suitable.[7] ABCD believes that, whilst care must be taken to avoid delaying insulin therapy in patients who clearly need it, there is a place for a carefully monitored trial of triple therapy in patients likely to be insulin resistant (e.g. the very obese) as well as those patients reluctant or unable to take insulin because of employment issues or other reasons.

Glitazone use, fluid retention and congestive cardiac failure

There is growing recognition that oedema and heart failure can occur in patients treated with glitazones, particularly when used with insulin. A working group of the American Diabetes Association and the American Heart Association evaluated these risks and has recently published guidelines.[8] These emphasise the importance of assessing the risks of fluid retention and congestive heart failure prior to starting a glitazone, advising patients to monitor for oedema and breathlessness, and withdrawing glitazones if congestive heart failure develops. We recommend that NICE incorporates similar guidance in the future.

Use with insulin (1.3)

Because of these concerns about the risk of heart failure, glitazones are currently contraindicated in patients on insulin therapy in Europe. Therefore neither NICE nor ABCD can currently recommend use of glitazones with insulin in the UK. Nevertheless, in anecdotal reports using glitazones 'off-label' some UK clinicians have found this combination useful in obese patients taking large doses of insulin; there can be improvements in blood glucose control and reductions in insulin dose.[9] If such use is considered, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction and to ensure that the patient understands and accepts the increased risk.

Hepatotoxicity (3.5)

The first glitazone, troglitazone, was withdrawn because of a widely publicised association with liver failure. To date, similar hepatotoxicity has not been observed with either pioglitazone or rosiglitazone; in fact improvement in liver function is sometimes reported. Recent changes to the licences in the US recommend that liver enzymes be monitored 'periodically' during treatment, although hepatic contraindications to glitazones are unchanged.

Furthermore, in non-alcoholic steatohepatitis (NASH), which is associated with insulin resistance, use of glitazones may be associated with significant improvement in biochemical and histological markers of liver disease.[10] Clarification of the cause of hepatic dysfunction is important before glitazones are initiated in patients with abnormal liver function tests. Currently, ABCD would only advise cautious use of glitazones in individuals with mild hepatic dysfunction known to be due to NASH. Intermittent monitoring of liver function is recommended in this scenario, not least to establish whether there is any improvement.

Further studies are required to establish whether monitoring of liver function tests every two months is clinically justified for all patients on glitazone therapy or should be reserved for those with abnormal liver function tests prior to the initiation of therapy.

Summary

The revised NICE guidance on the use of glitazones was published in 2003, only days before the extension to their product licences. The views of ABCD on this guidance and on the use of glitazones in the UK are as follows.

- Addition of a glitazone to metformin is the preferred second-line oral antidiabetic therapy in the obese.
- Glitazones should be considered in place of metformin in renal impairment.
- Glitazones should not be a substitute for insulin in patients with poor glycaemic control on maximum tolerated dose of sulphonylurea and metformin.
- Glitazones should be considered as monotherapy in those unable to take metformin.
- A carefully monitored trial of triple therapy (metformin, a sulphonylurea and glitazone) may be considered in the very obese, as well as those patients unwilling to consider insulin therapy.
- Caution is needed to monitor for fluid retention and heart failure, particularly in patients with renal disease and in patients on insulin.
- Use of glitazones with insulin cannot currently be recommended in the UK. However, if such use is considered by the clinician, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction and to ensure that the patient understands and accepts the increased risks.
- Clarification of the cause of hepatic dysfunction is important before glitazones are initiated in patients with abnormal liver function tests. Glitazones should be avoided in patients with pre-treatment serum transaminase levels >2.5 times the upper limit of normal or evidence of active liver disease.
- Cautious use of glitazone therapy may be considered in selected individuals with mild hepatic dysfunction known to be due to NASH, with regular monitoring of liver

function tests and observance of current indications for discontinuation of therapy.

• Further studies are required to establish whether two-monthly monitoring of liver function is clinically justified for all patients during glitazone therapy.

References

1. Bailey CJ, Day C, Krentz A. Nice timing for glitazones. *Br J Diabetes Vasc Dis* 2003; **3:** 308–309.
2. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. *BMJ* 2003; **326:** 4–5.
3. Lebovitz H, Dole JF, Patwardhan, *et al.* Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *JCEM* 2001; **86:** 280–288.
4. Aronoff SL, Rosenblatt S, Braithwaite S, *et al.* Pioglitazone hydrochloride monotherapy improves glycaemic control in the treatment of patients with type 2 diabetes: a 6-month randomised placebo-controlled study. *Diabetes Care* 2000; **23:** 1605–1611.
5. Morjaria HK, Lawrence IG, Jarvis J, *et al.* Clinical effectiveness of pioglitazone in triple therapy in type 2 diabetes mellitus. *Diabetic Med* 2002; **19**(Suppl 2): P42.
6. Kiayias JA, Vlachou ED, Theodosopoulou E, *et al.* Rosiglitazone in combination with glimepiride plus metformin in type 2 diabetic patients. *Diabetes Care* 2002; **25:** 1251–1252.
7. Levy D, James A, Liew L, *et al.* Prospective audit of triple therapy in poorly controlled Type 2 diabetes: enhanced response in South Asian people. *Diabetic Med* 2004; **21**(Suppl 2): A49.
8. Nesto RW, Bell D, Bonow RO, *et al.* Thiazolidinedione use, fluid retention and congestive heart failure. A consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 2004; **27:** 256–263.
9. Raskin P, Rendell M, Riddle MC, *et al.* A randomised trial of Rosiglitazone therapy in patents with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care* 2001; **24:** 1226–1212.
10. Promrat K, Lutchman G, Uwaifa GI, *et al.* A pilot study of pioglitazone treatment for non-alcoholic steatohepatitis. *Hepatology* 2004; **39:** 188–196.