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Oral hypoglycaemics

A review of the evidence

Background
The range of oral hypoglycaemic agents (OHAs) has increased from one insulin sensitiser (metformin) and one class of insulin secretagogues (sulphonylureas) with the addition of further class of insulin secretagogues (glitinides), a further class of insulin sensitisers (glitazones) and two new classes: an alpha glycosidase inhibitor and glucagon-like peptide agents. Recent data has influenced the recommended sequence and usage of OHAs and glycaemic targets.

Objective
This article reviews the recent evidence in type 2 diabetes about the pros and cons of oral hypoglycaemic agents and the benefits and costs of intensive glycaemic control. It suggests a stepwise approach to glycaemic control with OHAs according to the evidence base currently available.

Discussion
Before 2008, the recommended glycaemic management was healthy lifestyle, metformin and sulphonylurea if tolerated, then rosiglitazone or insulin. Pioglitazone could be used with insulin therapy but not as triple therapy. In 2007 and 2008 data about glitazones demonstrated a potential increased risk of myocardial infarction with rosiglitazone and increased risk of heart failure, peripheral fractures and macular oedema with both pioglitazone and rosiglitazone. In 2009 a new class of hypoglycaemic agents, glucagon-like peptide 1 agents, became available. Three trials published in 2009 failed to show a statistically significant reduction in cardiovascular events with intensive glycaemic management compared to conventional management. The current recommended target for HbA1c is <7% but higher or lower targets may be appropriate for individual patients.

Keywords: diabetes mellitus, type 2/therapy; glitazones; hypoglycemic agents

Before 2008 the recommended steps in glycaemic management were:

- healthy lifestyle
- metformin, sulphonylurea if tolerated, and finally
- consideration of a glitazone or insulin.[1]

The oral hypoglycaemic agents (OHAs) controlling postprandial glycaemia were not often used – meal time acarbose (Glucobay) slowing carbohydrate digestion or repaglinide (Novo Norm) transiently increasing prandial insulin secretion.

These recommendations were based on the pathophysiology of type 2 diabetes and the pharmacology of the then available OHAs. Healthy lifestyle improved insulin resistance, metformin and the glitazones reduced hepatic glucose output and increased peripheral glucose uptake, and the sulphonylureas increased insulin secretion. Only rosiglitazone was approved for Pharmaceutical Benefit Scheme (PBS) subsidy for use as triple therapy (with metformin and sulphonylurea) and pioglitazone was subsidised for use with insulin.

Evidence since late 2007 have changed our ideas about the pathophysiology of type 2 diabetes, the pharmacology of therapy and the recommendations for OHAs.

The glitazones

Before 2008, the pros and cons of glitazones seemed clear. Both rosiglitazone and pioglitazone could be given once daily and neither caused hypoglycaemia unless an insulin secretagogue or insulin was coprescribed. However, both were associated with increased subcutaneous fluid and fat accumulation and neither were recommended for those with symptomatic cardiac failure.[1,2]

In 2007 and 2008 some 'bad news' for both glitazones was published, particularly for rosiglitazone.

Myocardial infarction

Two large meta-analyses suggested a 40% increase in the incidence of myocardial infarction for patients treated with rosiglitazone compared to placebo.[3,4] However, the prospective open label Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study did not confirm this increase.[5] The Therapeutic Goods Association required modification to the prescribing information for rosiglitazone noting that the potential for increased risk of myocardial infarction should be taken

into account when choosing a glitazone.[6] The PBS subsidy for rosiglitazone as triple therapy (with metformin and sulphonylurea) or insulin was withdrawn but continued for dual therapy (sulphonylurea or metformin).

Pioglitazone did not get the same 'bad news' as rosiglitazone. A meta-analysis showed a reduction in the combined endpoint of death, myocardial infarction and strokes.[7] Pioglitazone is PBS subsidised for dual and triple therapy as well as with insulin therapy.

Cardiac failure

Three meta-analyses[3,4,8] and a subsequent open label trial[5] showed that the incidence of cardiac failure was increased for both pioglitazone and rosiglitazone, but the mortality from cardiac failure was not increased. However, the original studies excluded patients with any evidence of cardiac failure (rosiglitazone) or evidence of mild cardiac failure (pioglitazone). Given the known increase in the risk of cardiac failure in patients with no or minor cardiac failure, it has been suggested that any significant heart failure should be considered a contraindication to glitazone therapy.[9]

Fractures

A further review suggested that both rosiglitazone and pioglitazone were associated with increased rate of peripheral fractures (particularly in postmenopausal women).[10]

Macular oedema

There were postmarketing reports of new and worsening diabetic macular oedema with the glitazones.[6,11]

This bad news about the glitazones seems likely to reduce their use, particularly rosiglitazone which is now only available as dual therapy and has a 'black box' warning about its use in those with ischaemic heart disease.

Glucagon-like peptide and gliptins

It has been known for more than 30 years that insulin secretion is much higher when blood glucose is increased by an oral glucose load than if the same blood glucose increase is achieved with an intravenous glucose load (*Figure 1*).[12] This increase became known as the 'incretin effect' and was shown to be caused by gut neuro-hormonal responses to luminal food and food products.

The incretins[13] – glucagon-like peptide 1 (GLP_1) and glucose dependent insulinotrophic peptide (GIP) – are rapidly cleared from the circulation. For example, GLP_1 has a half life of 1–2 minutes, is rapidly broken down by an endothelial and circulating enzyme (di peptidylpeptidase 4, DPP4). The pharmaceutical industry has developed oral agents that block DPP4 and increase endogenous GLP_1 and GIP levels (the 'enhancers') and injected agents not affected by DPP4 but mimicking the effects of GLP_1 (the mimetics). At present the GLP mimetic available on the PBS requires injection (exenatide, Byetta).

Two of the gliptins (sitagliptin and vildagliptin) are currently subsidised by the PBS for use in patients with type 2 diabetes. They have the same hypoglycaemic effect as the other oral hypoglycaemic agents resulting in a decrease of HbA1c of 0.5–1.1%.[14] Side effects include nasopharyngeal symptoms and headaches. The gliptins are a new class of OHA and there is no long term data on safety. At present, gliptins are PBS subsidised for dual oral therapy with either sulphonylurea or metformin if the other agent is contraindicated or not tolerated.

Using the GLP agents

Early in 2008, if both metformin and sulphonylurea were indicated and tolerated, the next choice was between a glitazone (both rosiglitazone and pioglitazone were PBS subsidised for dual therapy) or insulin. In both cases many patients and doctors preferred continuing OHAs to starting insulin.

Acarbose (Glucobay) is not widely used and repaglanide (Novo Norm) is not effective if sulphonylurea is coprescribed. Rosiglitazone was initially PBS subsidised for triple therapy but this subsidy was withdrawn in 2008.

In 2009 the hypoglycaemic hierarchy changed.[1,15] If both sulphonylurea and metformin are suitable the guidelines suggest pioglitazone or insulin as the third step, both of which are PBS subsidised. If either metformin or a sulphonylurea is not suitable, the next step is either one of the glitazones, a gliptin or insulin, all of which are PBS subsidised for this indication.

The glitazones have become less attractive and insulin therapy more attractive. Doctors now have a third oral choice, a gliptin (sitagliptin or vildagliptin) (*Figure 2*). Exenatide is an injectable option.

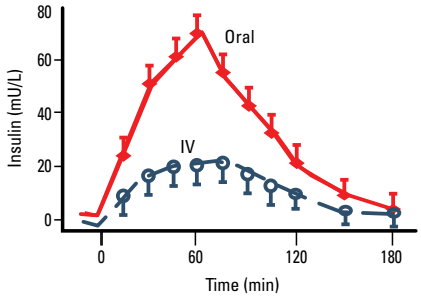

Figure 1. Insulin secretion – OGTT vs. IVGTT

HbA1c – is lower better?

Epidemiological analysis of follow up data from the United Kingdom Prospective Diabetes Study (UKPDS)[16] suggested that the benefit of lowering HbA1c in newly diagnosed patients with type 2 diabetes was a lower risk of long term micro- and macro-vascular complications. However, the UKPDS also showed that the costs of a lower HbA1c were weight gain and hypoglycaemia (as well as extra effort by both patient and doctor). Accordingly, most authorities suggest targets that offer a compromise between the benefits and costs of lowering HbA1c (*Table 1*). The Australian recommendation[1] of HbA1c <7% for most patients with type 2 diabetes is similar to targets for other countries. Given that most of the morbidity and mortality of long term diabetes complications is caused by macrovascular disease, three recently published trials were designed to test if lowering HbA1c below conventional targets would decrease cardiovascular events in patients at moderate to high risk.[17–19]

None of the three trials showed a statistically significant decrease in cardiovascular events in the intensive treated group compared to the conventional treated group. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a 20% increase in mortality occurred and the trial was stopped early.[17] In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial there was a nonsignificant increase,[18] and in the Veterans Affairs Diabetes Trial (VADT) trial, a nonsignificant decrease in cardiovascular events.[19]

For the time being, the current Australian target remains <7%. Lower targets might be appropriate for younger, recently diagnosed, otherwise healthy patients who are able to achieve lower targets

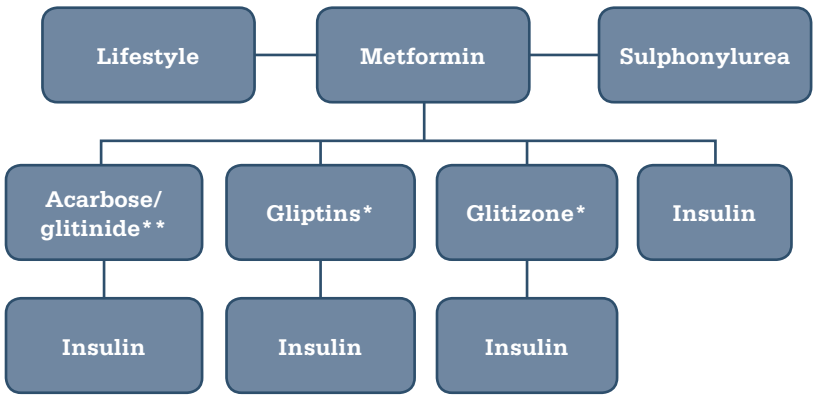

Figure 2. Stepwise management for type 2 diabetes mellitus

* If metformin or sulphonylurea is contraindicated or not tolerated gliptins and glitazones (pioglitazone and rosiglitazone) are PBS subsidised as dual therapy

** Glitanides are not effective with sulphonylureas

Table 1. Suggested glycaemic targets set by authorities

	Healthy	RACGP	ADA/EASD	AACE	IDF
HbA1c (%)	<6.0	<7.0	<7.0	<6.5	<6.5
FBG (mmol)	<5.5	4–6	3.9–7.2	<6.0	<6.0

RACGP = The Royal Australian College of General Practitioners
ADA/EASD = American Diabetes Association/European Association for the Study of Diabetes
AACE = American Association of Clinical Endocrinologists
IDF = International Diabetes Federation

(eg. <6% for newly diagnosed aged <40 years) and higher targets might be set for older patients with long standing diabetes and/or significant complications or comorbidities.[20]

Summary

Glitazones: in 2007 and 2008, concern was raised about the adverse effects of the glitazones. Rosiglitazone was reported as increasing myocardial infarctions by 40% and both rosiglitazone and pioglitazone were recognised as precipitating heart failure, causing peripheral fractures and possibly causing or worsening macular oedema.

Glucagon-like peptide and gliptins: glitazones, particularly rosiglitazone, are less attractive as dual therapy and only pioglitazone is PBS subsidised for triple therapy or with insulin. Sitagliptin and vildagliptin are newer classes of oral medications that inhibit the breakdown of endogenous GLP and enhance the glycaemic effects of endogenous GLP.

HbA1c and cardiovascular disease: the ACCORD, ADVANCE and VADT trials have shown no significant benefits of intensive over conventional treatment in terms of cardiovascular events. For the time being, it is generally recommended that the Australian target is an HbA1c <7%, but it is recognised that lower or higher targets may be appropriate for individual patients.

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