Combination treatment with insulin and oral agents in type 2 diabetes mellitus

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Abstract

The need to improve glycaemic control in type 2 diabetes has been reinforced by the United Kingdom Prospective Diabetes Study (UKPDS). Due to progressive deterioration of beta-cell function after diagnosis, oral hypoglycaemic agents often fail to maintain adequate glycaemic control after only a few years of treatment. This paper considers the treatment options available at this stage and reassures diabetologists that the combined use of insulin plus metformin with or without an added sulphonylurea is logical, is as effective as insulin alone, and provides superior weight regulation in many patients. A combination of metformin with glargine insulin seems particularly effective and well tolerated. The long-term advantages of such treatments in terms of clinical outcomes have yet to be demonstrated in clinical trials. 


Key words: insulin, oral antidiabetic agent, type 2 diabetes, metformin, sulphonylurea, thiazolidinedione, combination therapy.

Introduction

Conventional treatment of diabetes has focused on insulin for type 1 (insulin-dependent) patients and oral agents for type 2 (non-insulin-dependent) patients, each in addition to dietary and lifestyle changes. Recent studies have emphasized the need for good control of blood glucose and blood pressure, and reduction of elevated plasma lipid levels in both groups of patients to avoid long-term vascular and diabetic complications. Only in recent years has it become acceptable to give a combination of oral agents and insulin to control blood glucose. It has long been appreciated that at least short-term improvements in glycaemic control could be achieved in insulin-treated patients (with remaining C-peptide secretion) by adding glibenclamide. This review considers the evidence base for use of combinations of insulin and oral antidiabetic agents in the management of type 2 diabetes.

Rationale for insulin-based combination therapy

Pathophysiological and pharmacological considerations

Properties of the five main classes of oral antidiabetic agents (metformin, sulphonylureas, meglitinides, α-glucosidase inhibitors and TZDs) have been reviewed elsewhere. Table 1 provides a précis of the mechanisms and key features of the five classes of oral antidiabetic agents currently in clinical use. Of these, metformin and insulin secretagogues have been extensively studied in combination with insulin, and will provide the main focus of this article.

The main endocrine problems in type 2 diabetes are an absolute or relative deficiency of insulin, and the resistance of tissues to insulin action. These endocrinopathies lead to increased hepatic glucose output and reduced peripheral glucose utilization. The resulting hyperglycaemia is toxic to beta-cells, so the pathological state is intensified, and raised blood glucose levels occur both in the pre-prandial state and after meals. A reduction in the suppression of lipolysis by insulin increases circulating free fatty acids which further damage beta-cell function and insulin sensitivity. Accordingly, treatments that lower hyperglycaemia, especially in the fasting state, will help to improve insulin secretion and reduce other biochemical abnormalities. Insulin secretagogues are useful while some beta-cell function remains: measurement of C-peptide allows a simple assessment of remaining endogenous insulin secretion.
Role of insulin treatment in type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control (average 0.9% reduction of HbA1C) using sulphonylureas or insulin, significantly reduced microvascular complications. The incidence of myocardial infarction, the commonest cause of death for diabetic patients, was decreased by 16% (almost statistically significant p=0.052). Although physicians often aim for an HbA1C of 7–7.5%, insulin treatment seems the only way to improve diabetes control. Several management guidelines for type 2 diabetes are currently promoted, including a simplified ‘desk-top guide’ from the International Diabetes Federation relevant to clinical practice in Europe. When it is clear that multiple oral agents and lifestyle interventions are inadequate to control hyperglycaemia, complications or to achieve an HbA1C of 7–7.5%, insulin treatment seems the only way to improve diabetic control. However, the UKPDS and other studies have failed to demonstrate that starting insulin treatment necessarily achieves superior control of HbA1C. The initial options when starting insulin treatment are therefore to switch to insulin alone, or to add insulin therapy to existing oral agents. A combination of insulin with an insulin sensitiser may be rational. Indeed, metformin has been shown to be cardioprotective in overweight type 2 diabetic patients, and it has been suggested that the addition of metformin to insulin may help to offset any putative increase in cardiovascular risk that may be associated with insulin treatment. Fewer studies have examined TZDs in combination with insulin, and concerns remain over the possibility of fluid retention and cardiac failure in this setting.

Clinical experience with insulin-based combination therapy

Insulin + insulin sensitisers

There is increasing evidence to suggest that a combination of oral agents and insulin produces as good, if not better, diabetic control than insulin alone. Several studies have evaluated the addition of one injection of isophane insulin at bedtime to oral agents. The availability of a wider range of insulin treatments has

<table>
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<th>Table 1. Properties of principal classes of oral antidiabetic agents</th>
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<td><strong>Class</strong></td>
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**Abbreviations**

- HbA<sub>1C</sub>: haemoglobin A<sub>1C</sub>
- PPAR<sub>γ</sub>: peroxisome proliferator-activated receptor-gamma
- TZDs: thiazolidinediones

The initial options when starting insulin treatment are therefore to switch to insulin alone, or to add insulin therapy to existing oral agents. If insulin is used alone then any regimen could be chosen, from a twice-daily injection regimen using isophane insulin, to twice-daily, ready-proportioned mixtures of short-acting and isophane insulin. Newer insulin analogues or a four-times daily basal-bolus injection regimen can also be used. In principle, any oral antidiabetic agent can be combined with insulin, although sulphonylureas or meglitinides require sufficient remaining beta-cell function to influence glycaemia. The vast majority of patients with late-stage, insulin-requiring type 2 diabetes will be overweight and/or markedly insulin resistant, so a combination of insulin with an insulin sensitiser may be rational. Indeed, metformin has been shown to be cardioprotective in overweight type 2 diabetic patients, and it has been suggested that the addition of metformin to insulin may help to offset any putative increase in cardiovascular risk that may be associated with insulin treatment. Fewer studies have examined TZDs in combination with insulin, and concerns remain over the possibility of fluid retention and cardiac failure in this setting. The following section reviews clinical experience with combinations of oral antidiabetic agents and insulin in type 2 diabetes.
Significant placebo-corrected reductions in total cholesterol (1.0 [95% CI 0.1–1.9] mmol/L) and LDL-cholesterol (1.0 [0.1–1.9] mmol/L) were also observed in the metformin group in one of the studies, and the overall reduction in total cholesterol for both groups was 0.6 (0.1–1.1) mmol/L. These observations are consistent with the many observations of improved lipid profiles in metformin-treated patients.

Substitution of metformin with another class of oral antidiabetic agent may not improve glycaemia, as shown in an open-label trial in 80 patients with type 2 diabetes already receiving bedtime NPH insulin + metformin (850–1,000 mg/day). The patients were randomised to 13 weeks of treatment with repaglinide 12 mg/day or metformin at the previous dose. Insulin was titrated to achieve a fasting blood glucose target of ≤ 6.0 mmol/L. HbA1C improved modestly in the metformin group, from 8.4% to 8.1%, but deteriorated in the repaglinide group, from 8.1% to 8.6% (p=0.005 between groups). Patients receiving metformin also gained less weight (mean 0.9 kg) compared with repaglinide (mean 2.7 kg, p=0.002 between treatments). Diabetes Treatment Satisfaction Questionnaire scores improved for metformin and decreased for repaglinide.

Mechanisms underlying the minimisation of weight gain with metformin-insulin regimens are complex. Less glycosuria with lower blood glucose levels leads to weight gain and may reduce metabolic rate. This is offset by the reduction in gluconeogenesis and possibly reduced energy intake during metformin treatment.

TZDs are also insulin sensitisers, and insulin has been studied in combination with these agents, although TZDs are not licensed for use in combination with insulin in Europe. One study compared the effects of insulin alone, troglitazone plus insulin, and insulin plus metformin in 88 patients previously treated with insulin with a mean HbA1C of 8.7% at baseline.24 The largest effects on HbA1C occurred in the insulin plus troglitazone group (final HbA1C 6.4%) compared with insulin alone (final HbA1C 7.0%) and on insulin plus metformin (final HbA1C 7.1%). A significant reduction in the average insulin dose of 12.8 units/day occurred in the troglitazone group, compared with a reduction of 1.4 units/day in the metformin group. On the other hand, patients on combined treatment with troglitazone gained 4.4 kg on average whilst the metformin group gained only 0.5 kg. Although troglitazone has been withdrawn from clinical use due to hepatotoxicity, its effects on glycaemia and body weight indicate effects of the thiazolidinedione class.

Triple therapy with two insulin sensitisers, metformin and rosiglitazone, was evaluated in a recent, randomised study in 16 obese type 2 diabetic patients previously poorly controlled on regimens based on NPH insulin.25 HbA1C did not change in the patients randomly assigned to remain on insulin alone, but declined from 8.8% to 6.8% in the group randomised to triple therapy. This improvement was driven by improved insulin sensitivity in the triple therapy group versus control.

### Insulin + other oral antidiabetic agents

Studies evaluating newer oral hypoglycaemic agents in combination...
tion with insulin are in progress. One such study compared NPH insulin at bedtime with either gliclazide 160 mg twice daily or repaglinide 4 mg three times daily in 80 type 2 diabetic patients over a 13-week period. No significant difference was found between groups in the average insulin dose, mean weight change, mean HbA1C reduction or the number of hypoglycaemic episodes.

Combining bedtime NPH insulin plus acarbose at mealtimes results in moderate reductions in HbA1C of 0.4–0.7%. This combination may be useful for obese patients with contra-indications to metformin, or unable to tolerate this agent. However, higher doses of acarbose are associated with a high incidence of gastrointestinal side effects.

In another study, 145 obese diabetic patients with poor diabetic control on oral agents were assigned suppurtime 30/70 short-acting and NPH insulin mixture with either twice-daily gliclazide 8 mg or placebo. Patients on gliclazide plus insulin achieved identical HbA1C reductions of 2% and fasting blood glucose values of 7.5 mmol/L compared with the insulin alone treated group. However, compared with the insulin alone group, the insulin-glimepiride group needed 40% less insulin, had less hypoglycaemia and fewer patients discontinued treatment prematurely (3% versus 15% on insulin alone).

**Optimising insulin-based combination regimens**

**Which insulin regimen?**

Daily glycaemic profiling reveals that the most severe hyperglycaemia in insulin-treated patients tends to occur after evening meals and at bedtime. This deficiency in diabetic control has been improved by the use of glargine insulin at bedtime. The longer duration of action of this new insulin analogue permits the use of higher doses to reduce blood glucose levels after evening meals and prior to bedtime. This also results in fewer early morning hypoglycaemic attacks, in contrast to the practice of increasing the dose of bedtime NPH insulin to gain better glycaemic control during the next day. Another advantage of the long half-life of glargine insulin is that this formulation can be given at any time of the day.

Evidence to support the utility of glargine insulin in combination with oral antidiabetic therapy comes from two well-designed clinical trials. In the first trial, 426 type 2 diabetic patients poorly controlled on oral antidiabetic therapy were randomised to receive additional glargine or bedtime NPH insulin, for 12 months, with their oral regimen unchanged. The second study, the ‘Treat-to-Target Trial’, involved randomisation of 756 type 2 diabetic patients poorly controlled on one or two oral agents to additional glargine or bedtime NPH insulin for 24 weeks. Once again, the doses of the oral agents were unchanged. The blood glucose-lowering efficacy of the different regimens was comparable in each study (table 2). However, there was significantly less hypoglycaemia with glargine insulin than NPH (table 2). Importantly, both studies showed that glargine insulin was associated with significantly less nocturnal hypoglycaemia than NPH insulin.

A combination of bedtime insulin, as either NPH or glargine plus metformin, therefore appears to represent a good option for initiating insulin-based combination treatment, with recent evidence appearing to favour glargine. The advantages include minimal weight gain, and an insulin sparing effect of around 32% with metformin plus insulin. Sulphonylureas plus insulin have an insulin sparing effect of 42%, and when metformin and a sulphonylurea are combined with bedtime insulin a 62% insulin sparing effect is observed. This suggests that even if patients respond poorly to one oral agent given with insulin, the combination of two agents plus insulin may give a clinically useful insulin sparing effect.

**Potential difficulties**

Insulin combined with oral agents can successfully improve overall glycaemia, but blood glucose values after meals may not be well controlled. One such patient was treated with gliclazide 3 mg daily for eight months with a once-daily injection of glargine insulin in the morning. His dose of insulin rose from 55 units/day to 134 units/day over a six month period but his HbA1C fell from 9.6% to 6.9%. Whilst fasting blood glucose was generally well controlled, postprandial blood glucose values were frequently high (figure 2). On the one hand, the UKPDS suggested that a fall in HbA1C should reduce the risk of diabetic complications. On the other hand, the Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe (DECODE) study warns that high post-prandial blood glucose levels may cause vascular complications. Furthermore, post-prandial hyperglycaemic oxidative stress may damage the vascular endothelium, an early event in the process of atherogenesis. A recent report also suggests that post-prandial hyperglycaemia may be the main contributor to increased HbA1C.

**Who should receive insulin and oral agent in combination?**

The UK National Service Framework for Diabetes: Standards’ goal for HbA1C is 6.5–7.5%, although treatment must be indi-
vidualised according to the patient's age, presence of diabetic complications and ability to achieve the target. The importance of lifestyle changes, including diet and exercise, must always be reinforced. A patient with a BMI > 25 kg/m² may usefully be treated initially with metformin if there are no contraindications to its use. The dose should be slowly titrated to a maximum tolerated dose (whichever is the lower) up to 1,000 mg three-times daily. Dose reductions help some patients to tolerate this treatment. Alternative treatments include acarbose or a thiazolidinedione.

A sulphonylurea can be added where HbA1c remains > 7.5% and the fasting blood glucose > 6 mmol/L with the dose adjusted according to efficacy and tolerability. If this combination fails to achieve target values then a bedtime dose of insulin or a once-daily dose of glargine can be started at an initial dose of 10 units/day. Patients should be advised to slowly increase the insulin dose by two unit increments every three days, as required, to reach their fasting morning blood glucose target. Unresponsive obese patients may need more than 100 units/day and up-titrated by 5 units/day increments. The sulphonylurea dose can be reduced, or the drug withdrawn, if hypoglycaemia is a frequent problem.

For patients intolerant to or unsuitable for metformin, a sulphonylurea with or without additional acarbose can be tried. If after six months of this combined treatment the control targets are not met then a change to twice daily or more injections of insulin daily should be tried. Metformin should be continued if possible to minimise weight gain and insulin requirement.

Unfortunately, many patients are reluctant to start injection treatment and fear hypoglycaemia and weight gain. These patients may be particularly amenable to trying a regimen based on one insulin injection daily in combination with oral agents.