Intensive insulin therapy in type 1 and type 2 diabetes

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Intensive insulin regimens can produce substantial clinical benefits for patients with type 1 and type 2 diabetes, but they are associated with an increased incidence of hypoglycaemia. This article discusses such regimens and whether the risk of hypoglycaemia can be reduced by using the new basal insulin analogue, insulin glargine.

The key aim of diabetes treatment is to lower blood glucose concentrations to near normal to prevent diabetes-associated complications. The ultimate agent for achieving good glycaemic control is insulin, either by improving insulin sensitivity (lifestyle changes or pharmacologically), or by increasing insulin levels (increasing pancreatic insulin output or insulin replacement). The importance of glycaemic control and intensive insulin replacement strategies to prevent diabetes complications is established for patients with type 1 diabetes (Diabetes Control and Complications Trial Research Group, 1993). Improving glycaemic control in patients with type 2 diabetes also reduces the risk of microvascular complications, although the evidence that it reduces macrovascular complications is less strong (Andersson and Svärdsudd, 1995; UK Prospective Diabetes Study (UKPDS) Group 1998a). The most effective way of achieving tighter glycaemic control in type 2 diabetes also needs to be established.

Diabetes is associated with a wide range of micro- and macrovascular complications. Microvascular complications include: retinopathy, which can lead to blindness; neuropathy, often resulting in foot ulcers or even amputations in severe cases; and nephropathy, which can lead to renal failure. Macrovascular complications include coronary artery disease and stroke, which are frequent causes of premature mortality in patients with diabetes, and peripheral vascular disease, increasing the risk of amputation. It is now widely acknowledged that there is a clear relationship between the degree of hyperglycaemia and the risk of diabetic complications (Klein, 1995; Klein et al, 1996; Stratton et al, 2000).

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EFFICACY OF INTENSIVE TREATMENT REGIMENS

The benefits of intensive therapeutic goals were illustrated by the results of two pivotal, long-term studies, the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes and the UKPDS in patients with type 2 diabetes. These trials showed that improved glycaemic control reduces the risk of microvascular complications, and also provided some evidence for a potential reduction in risk of macrovascular complications (DCCT Research Group, 1993; UKPDS Group, 1998a).

The DCCT

The DCCT compared intensive with conventional insulin therapy in 1441 patients with type 1 diabetes. Of these, 726 patients had no retinopathy at the start of the study (the primary-prevention cohort) and 715 had mild retinopathy (the secondary-intervention cohort). Intensive therapy involved the administration of insulin three or more times daily by injection (or by an external pump) compared with one or two daily injections (conventional therapy). Patients receiving intensive therapy had their insulin dosages adjusted daily to achieve predetermined treatment goals and visited their study centre each month. Patients were contacted even more frequently by telephone. Treatment goals included preprandial blood glucose concentrations between 3.9 and 6.7 mmol/litre, postprandial concentrations of <10 mmol/litre and haemoglobin A_{1c} (HbA_{1c}) levels within the normal range (< 6.05%).

A total of 44% of patients in the intensive therapy group achieved the HbA_{1c} target of 6.05% or less at least once, although less than 5% maintained an average value in this range. The mean

value for all glucose profiles in the intensive therapy group was 8.6±1.7 mmol/litre compared with 12.8±3.1 mmol/litre in the conventional therapy group (DCCT Research Group, 1993).

Results from this study showed that intensive therapy significantly delayed the onset and slowed the progression of microvascular complications. For patients receiving intensive therapy the adjusted mean risk of developing retinopathy was reduced by 76% in the primary-prevention cohort, and the progression of retinopathy was slowed by 54% in the secondary-prevention cohort, compared with those treated conventionally. Additionally, in the two cohorts combined, the risk of occurrence of albuminuria was reduced by 56% and that of clinical neuropathy by 60%. Intensive therapy also reduced the risk of macrovascular complications by 41%, although this was not significant. However, the relative youth of the patients may have influenced this finding, by making the detection of differences in rates of macrovascular complications unlikely (DCCT Research Group, 1993).

The UKPDS

Started in 1977, the UKPDS was designed to establish whether intensive glycaemic control reduced the risk of micro- and macrovascular complications in patients with type 2 diabetes compared with conventional therapeutic goals. Patients in the intensive group had the predetermined therapeutic goal of fasting plasma glucose concentrations of less than 6 mmol/litre and were randomized to receive insulin or sulphonylureas as initial treatment. For patients in the conventional group, the goal was the best achievable fasting plasma glucose concentrations with diet alone; drugs were added only if patients experienced symptomatic hyperglycaemia or fasting plasma glucose concentrations rose above 15 mmol/litre. Patients were also separated according to body weight. Non-overweight patients (≤120% of ideal body weight) with intensive goals were randomized to receive insulin administered daily (30%) or sulphonylureas (either chloropropamide, glibenclamide or glipizide) given daily (40%). The remaining patients received conventional treatment with diet (30%).

Overweight patients with intensive goals were also randomized to receive insulin (24%) or sulphonylureas (32%), but some patients also received metformin (20%). The remaining overweight patients received conventional treatment with diet (24%) (UKPDS Group, 1998a).

Over a median follow-up period of 10 years, patients treated intensively with sulphonylureas or insulin had average HbA_{1c} levels of 7.0% compared with 7.9% in the conventional group. Additionally, these patients had a significant (25%) decrease in risk of microvascular complications. The risk of macrovascular complications for patients receiving intensive therapy was also reduced – there was a 16% risk reduction for myocardial infarction – but not significantly (UKPDS Group, 1998a). Overweight patients receiving intensive metformin therapy had average HbA_{1c} levels of 7.4% and a risk reduction of 32% for any diabetes-related endpoint, compared with those receiving conventional treatment.

The metformin group also had a significantly lower risk (36%) of all-cause mortality than the conventional group, and also than those treated with sulphonylureas or insulin. The patients receiving metformin also had a lower risk of diabetes-related death than the conventional group, although there were no significant differences compared with the other intensively-treated patients (UKPDS Group 1998b).

Importantly, epidemiological analysis of the results for all UKPDS patients showed that for any 1% reduction in HbA_{1c} there was a 37% decrease in risk for microvascular complications and a 21% decrease in the risk of any diabetes-related endpoint or death (*Figure 1*) (Stratton et al, 2000).

BARRIERS TO IMPLEMENTING INTENSIVE REGIMENS

Although intensive therapeutic goals are beneficial in reducing the risk and progression of diabetic microvascular complications, there are significant drawbacks to current intensive regimens that have limited their optimal implementation. One is the need for complex regimens that may impact more on lifestyle and therefore may be difficult for patients to adhere to.

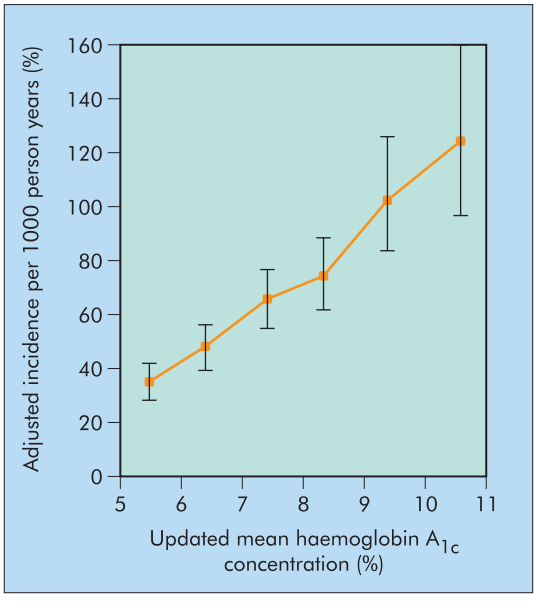


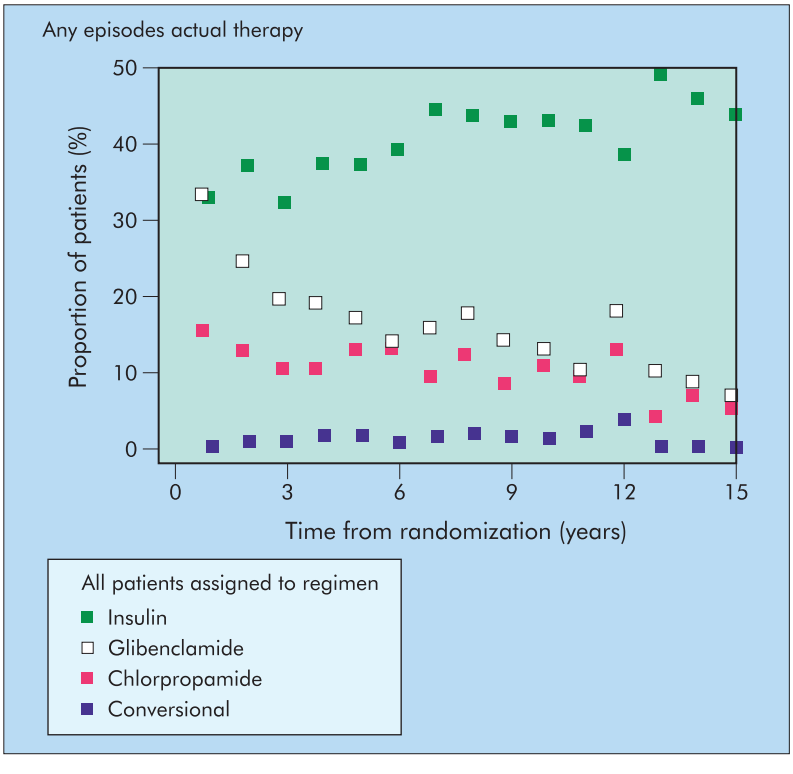
Figure 1. Incidence rate of any diabetes-associated complication with decreasing haemoglobin A_{1c} levels (Stratton et al, 2000).

Additionally, intensive regimens have also been associated with significantly higher treatment-related adverse events, such as weight gain and hypoglycaemia, than conventional therapy.

In the DCCT, patients receiving intensive therapy had a 33% higher risk of becoming overweight and, after 5 years, these patients had gained a mean 4.6 kg more than patients receiving conventional therapy. The incidence of severe hypoglycaemia (patients requiring assistance to receive treatment for hypoglycaemia) was also approximately three times higher in the intensive therapy group (62 hypoglycaemic episodes per 100 patient years) than in the conventional therapy group (19 hypoglycaemic episodes) (DCCT Research Group, 1993).

Similarly, results from the UKPDS show that weight gain was significantly higher for patients receiving intensive therapy (mean 2.9 kg) than in the conventional group; patients receiving insulin gained more weight (4.0 kg) than patients receiving chlorpropamide (2.6 kg) or glibenclamide (1.7 kg) (UKPDS Group, 1998a). However, patients receiving metformin as part of an intensive regimen did not gain significantly more weight compared with the conventional group, suggesting that this could be a useful treatment strategy in such patients (UKPDS Group, 1998b).

Figure 2. Incidence of any hypoglycaemic episodes in conventionally treated patients and patients receiving intensive treat-to-target therapy with insulin or sulphonylureas (UK Prospective Diabetes Study Group, 1998a).



In the UKPDS, hypoglycaemia also occurred significantly more frequently in the intensive group than the conventional group. Although hypoglycaemia was more common with insulin therapy, it was also a problem in patients receiving sulphonylureas (*Figure 2*) (UKPDS Group, 1998a). Over 10 years of follow up, the proportion of patients per year who experienced any hypoglycaemic episode were: conventional group (0.9%), chloropropamide group (12.1%), glibenclamide group (17.5%), insulin group (34.0%) and metformin group (4.2%) (UKPDS Group, 1998b).

IMPACT OF HYPOGLYCAEMIA ON PATIENTS

To an extent, occasional episodes of hypoglycaemia appear to be accepted as the price to be paid for improved glycaemic control. However, the effects of hypoglycaemia can be severe. Symptomatically, hypoglycaemia ranges from mild, with symptoms arising from adrenergic stimulation (tachycardia, tremor, sweating), to severe, with symptoms of neuroglycopaenia (altered consciousness level) and leading to loss of consciousness.

Insulin is often given at bedtime, which can contribute to patients developing nocturnal hypoglycaemia. This may also lead to a lack of awareness of early warning signs of hypoglycaemia at other times (Hepburn et al, 1990).

These hypoglycaemic attacks are very frightening for patients and their families, leaving patients feeling scared and vulnerable, and lead to a reduction in their quality of life. It is, however, their long-term effects on patients' quality of life that is most important. The constant fear felt by patients of experiencing another 'hypo' can place significant strains on their family relationships and can severely impair a patient's lifestyle, through interfering with their ability to perform everyday tasks and by causing depression in some patients. Unsurprisingly, therefore, hypoglycaemia is an important limiting factor of intensive therapy and prevents many patients from achieving their glycaemic targets (UKPDS Group, 1998a).

IMPACT OF HYPOGLYCAEMIA ON THE NHS

Hypoglycaemia has a significant impact on the NHS in terms of health professionals' time and cost of treatment. Although the precise costs are not known, a study in Tayside, Scotland, has provided an estimate of the cost of severe hypoglycaemia (requiring emergency assistance). Over a 12-month period, a total of 244 episodes of

severe hypoglycaemia, in 160 patients, were recorded. Of these cases, 7.1% were patients with type 1 diabetes, 7.3% were patients with type 2 diabetes treated with insulin and 0.8% were patients with type 2 diabetes treated with oral hypoglycaemic agents (OHAs). The estimated cost of emergency treatment for these patients was calculated as £92 078. By extrapolating these results for the whole of the UK, the authors estimate that the emergency cost to the NHS of treating severe hypoglycaemia is £12 million per year (Morris et al, 2002).

OPTIMIZING INTENSIVE INSULIN THERAPY

Hypoglycaemia and weight gain have limited the success of intensive insulin replacement therapy. It is increasingly acknowledged that the unsatisfactory pharmacokinetics of older basal insulins, such as neutral protamine Hagedorn (NPH) and Ultralente insulins, play an important role in causing hypoglycaemia (Lepore et al, 2000; Vajo and Duckworth, 2000).

Although NPH and Ultralente have been useful treatment options they have not enabled health-care professionals to optimize intensive insulin therapy. This is because their characteristics fail to meet that of an ideal basal insulin, with both NPH and Ultralente having an early peak level of activity (Lepore et al, 2000). Nocturnal hypoglycaemia, therefore, remains a problem as these insulins peak during the night following bedtime administration. Additionally, their subsequent diminishing activity means that patients are at risk of elevated glucose concentrations at breakfast time – the 'dawn' phenomenon. The fact that these insulins do not have a true 24-hour duration of action means that some patients need to inject a basal insulin twice daily. This impacts adversely on patient compliance, interferes with lifestyle and leads to poor glycaemic control. There is also variability of absorption with older basal insulins, particularly Ultralente, from patient to patient and between injection sites (Lepore et al, 2000; Vajo and Duckworth, 2000).

Long-acting basal insulin analogues

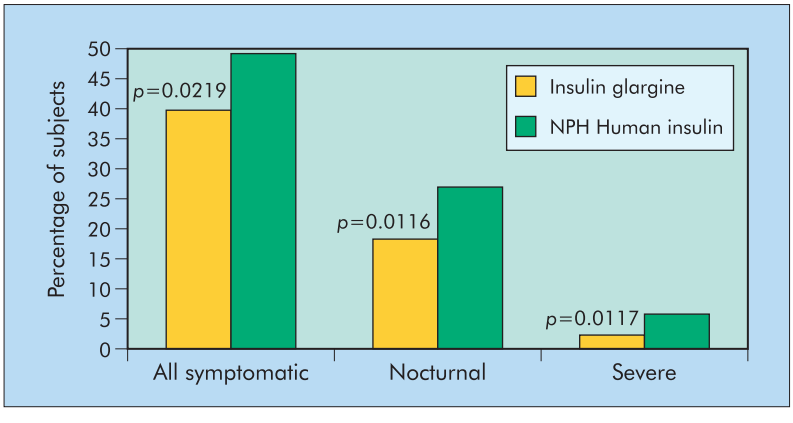
The recent development of novel long-acting insulin analogues potentially offers a viable alternative to older basal insulins. Insulin detemir (Novo Nordisk, Bagsvaerd) is currently undergoing clinical trials, but insulin glargine (Aventis Pharma, Frankfurt am Main) became available in the UK in August 2002, and has been available in the US since May 2001 (McKeage and Goa, 2001; Owens et al, 2001).

Insulin glargine is a modified version of endogenous insulin, produced by recombinant DNA technology. Upon subcutaneous injection, insulin glargine crystallizes to form hexamers that have greater stability than other basal insulins, giving delayed and predictable absorption (Owens et al, 2001). Owing to this stability, insulin glargine has a prolonged, 24-hour duration of action and a flat 'peakless' pharmacokinetic profile that closely resembles that of endogenous basal insulin secretion. This extended duration of action allows once-daily administration that is more convenient for both patients and health-care professionals.

Trials in patients with type 1 diabetes have shown that insulin glargine, injected once daily as part of a basal-bolus regimen, results in significantly lower fasting blood glucose (FBG) compared with NPH, and is at least as effective as NPH at lowering HbA_{1c} (Pieber et al, 2000; Raskin et al, 2000; Rosenstock et al, 2000). Patients receiving insulin glargine have significantly fewer episodes of symptomatic, nocturnal and severe hypoglycaemia compared with NPH insulin (*Figure 3*) (Ratner et al, 2000). Insulin glargine has also been associated with significantly less weight gain in patients with type 1 diabetes. Furthermore, in a 16-week study that compared once-daily insulin glargine and once- or twice-daily NPH, in a basal-bolus regimen, average weight gain was significantly lower with insulin glargine (0.12 kg) compared with NPH (0.54 kg) (Raskin et al, 2000).

Similar findings have been observed for patients with type 2 diabetes. Insulin glargine, administered once daily, with or without bolus insulin, reduces HbA_{1c} levels and FBG concentrations to a similar level as once- or twice-daily administration of NPH, but with a significantly lower risk of nocturnal hypoglycaemia (Rosenstock et al, 2001). In a study where

Figure 3. Incidence of hypoglycaemia in patients receiving intensive regimens of insulin glargine or neutral protamine Hagedorn (NPH) (Ratner et al, 2000).



patients received bedtime administration of insulin glargine or NPH, in combination with OHAs, patients receiving insulin glargine had significantly lower post-dinner glucose concentrations than with NPH (Yki-Järvinen et al, 2000). In a study of 756 insulin-naïve patients with type 2 diabetes, comparing the ability of intensive regimens of insulin glargine and NPH (both combined with OHAs) to restore glycaemic control, almost 60% of patients in both groups reached their target HbA_{1c} levels of <7%. Importantly, the incidence of nocturnal hypoglycaemia was significantly lower with insulin glargine compared with NPH (Rosenstock and Riddle, 2002).

Additionally, in a comparative study of once-daily insulin glargine and once- or twice-daily NPH in patients with type 2 diabetes, the average weight gain was significantly less with insulin glargine (0.4 kg) compared with NPH (1.4 kg) (Rosenstock et al, 2001).

CONCLUSIONS

Intensive therapy leads to significantly reduced incidence and delayed progression of microvascular complications in patients with type 1 and type 2 diabetes, and there is some evidence that intensive therapy may also reduce the incidence of macrovascular complications. However, up to now, the optimal implementation of intensive insulin regimens has been limited by the associated side effects of older basal insulin preparations, most notably weight gain and hypoglycaemia. The use of insulin glargine in intensive insulin regimens is likely to reduce the incidence of hypoglycaemia, helping patients to achieve glucose targets and, in the long term, to reduce the incidence of diabetic complications. HM

Conflict of interest: Dr Dean and Dr Sharp have received honoraria for professional advice and expenses for educational events from Aventis Pharma and Novo Nordisk.

KEY POINTS

- Intensive therapies delay the onset and progression of microvascular complications.
- Intensive therapy is associated with treatment-related complications, notably the risk of hypoglycaemia and weight gain.
- Hypoglycaemia is the major limiting factor of intensive therapy and prevents many patients from achieving optimal glycaemic control.
- Severe hypoglycaemic episodes have a significant impact on patients and health services.
- The unsatisfactory pharmacokinetics of older basal insulins is an important causative factor for these complications.
- Novel long-acting basal insulins have the potential to minimize such risks and advance insulin therapy.

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