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Hypoglycaemia in patients with type 2 diabetes: minimising the risk

MILES FISHER

Abstract

Achieving optimal glycaemic control is a priority for the management of diabetes and among patients with type 2 diabetes, it is increasingly becoming apparent that hypoglycaemia is a barrier to this. Hypoglycaemia can be associated with acute and long-term morbidity and is potentially fatal. Strategies to minimise the risk of hypoglycaemia in patients with type 2 diabetes are outlined here, including the need for patient education and optimisation of current treatments.

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Key words: hypoglycaemia, risk, type 2 diabetes

Introduction

In patients with type 2 diabetes the primary treatment goal is to effectively control blood glucose levels, which minimises the risk of long-term complications.1 The recent introduction of lower Hba1c targets as part of the QOF (from Hba1c < 7.5% to < 7.0%) highlights the shift towards tighter glycaemic control.2 However, hypoglycaemia and the fear of hypoglycaemia are increasingly becoming major barriers to achieving these goals.3,4

Hypoglycaemia is conventionally associated with type 1 diabetes, especially in relation to insulin treatment, and until recently was only considered a minor problem in the treatment of type 2 diabetes.5 However, it is becoming increasingly clear that the frequency of hypoglycaemic events in patients with type 2 diabetes may have been underestimated, partly due to limited symptom recognition in elderly patients.5 Minimising the risk of hypoglycaemia is therefore an important consideration in the treatment of type 2 diabetes. In this article, current thinking is discussed in the context of strategies to reduce the risk of hypoglycaemia in these patients.

Pathophysiology and symptoms

In individuals without diabetes, the initial response to a decline in blood glucose levels is suppression of insulin secretion, followed by the release of counter-regulatory hormones such as glucagon and adrenaline. Symptoms of hypoglycaemia become apparent at arterial blood glucose concentrations between 3.2 and 2.8 mmol/L.6 In patients with well-controlled type 2 diabetes, release of counter-regulatory hormones and hypoglycaemia symptom onset occur at higher blood glucose concentrations than in non-diabetic individuals, which may serve as a protective mechanism against severe hypoglycaemia.7,8 However,
in patients with poorly controlled type 2 diabetes requiring insulin therapy, the counter-regulatory response to falling blood glucose levels is diminished and symptoms of hypoglycaemia are reduced and do not appear until blood glucose levels are lower than in non-diabetic individuals. This situation is similar to that observed in patients with type 1 diabetes and contributes to impaired awareness of hypoglycaemia.7,9

Symptoms of hypoglycaemia can be considered as autonomic (sweating, palpitations, tachycardia, shaking, hunger), neuroglycopenic (confusion, drowsiness, uncoordination, speech difficulties) and malaise (nausea and headache).3,10,11 However, symptoms of hypoglycaemia vary from person to person, and are influenced by age, degree of glycaemic control and duration of diabetes.11–13 For simplicity, the generally accepted clinical categories of hypoglycaemia in the UK are ‘asymptomatic’ (biochemical), ‘mild’ and ‘severe’ (table 1).6,12,14

**Epidemiology**

The UK Hypoglycaemia Study Group has evaluated the incidence of hypoglycaemia in type 2 diabetes patients over a 9–12-month period.15 For those patients taking only OADs, the mean incidence of mild hypoglycaemia was 1.92 events/patient per year and for severe hypoglycaemia this was 0.1 events/patient per year. Patients taking insulin for < 2 years reported mild and severe hypoglycaemia incidences of 4.08 and 0.1 events/patient per year, respectively. For those patients using insulin for > 5 years, the rates of mild and severe hypoglycaemia were higher, at 10.2 and 0.7 events/patient per year.15

The projected increase in the incidence of type 2 diabetes16 may act to increase the absolute number of hypoglycaemic episodes reported, while more frequent use of insulin to reach target blood glucose concentrations17 may increase the incidence of hypoglycaemia.

**Causes and risk factors**

Hypoglycaemia in people with type 2 diabetes is commonly iatrogenic, i.e. caused by glucose-lowering treatments.18 However, the risk of experiencing hypoglycaemia can be modified by a number of other factors (table 2).

**Antidiabetic drug therapies**

The risk of hypoglycaemia with OAD therapy is variable and is dependent on the pharmacokinetic and pharmacodynamic profile of an individual drug, which may be influenced by polypharmacy (drug–drug interactions) and variations in food intake (e.g. missed meals).14,19,20

**Insulin secretagogues**

SU therapy is one of the key causes of hypoglycaemia in type 2 diabetes, as these drugs increase insulin output from the pancreas. The risk of hypoglycaemia with each SU relates to its pharmacokinetic properties and is greatest with long-acting SUs such as chlorpropamide and glibenclamide.19 Conversely, the newer shorter-acting SUs such as glipizide are associated with a much lower hypoglycaemic potential.14,19 The prandial glucose regulators (e.g. repaglinide, nateglinide), a second class of insulin secretagogues, have relatively low hypoglycaemic potential6,19 with seemingly negligible activity at low blood glucose concentrations.

**Table 1. Definitions of hypoglycaemia**

<table>
<thead>
<tr>
<th>Hypoglycaemia severity</th>
<th>Definition6,14</th>
<th>Management12,14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Hypoglycaemia (blood analysis showing low blood glucose concentrations) with no symptoms and no impairment of consciousness</td>
<td>On diagnosis this can be self-managed oral intake of glucose tablets, gel or sugary foods (if blood glucose measured)</td>
</tr>
<tr>
<td>Mild</td>
<td>Associated with symptoms the patient is able to self-treat</td>
<td>Self-managed oral intake of glucose tablets, gel or sugary foods</td>
</tr>
<tr>
<td>Severe/profound</td>
<td>Patient requires urgent assistance</td>
<td>Medical emergency – requires urgent assistance: intravenous glucose or glucagon administration</td>
</tr>
</tbody>
</table>

**Table 2. Causes and risk factors for hypoglycaemia18**

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Factors that may increase the risk of hypoglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin therapy</td>
<td>Impaired awareness of hypoglycaemia</td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td>Increasing age</td>
</tr>
<tr>
<td></td>
<td>Increasing duration of diabetes</td>
</tr>
<tr>
<td></td>
<td>Impaired drug clearance due to renal and/or hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>Impaired counter regulatory capacity</td>
</tr>
<tr>
<td></td>
<td>Decreased hepatic glucose production – secondary to liver failure, alcohol intake</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose absorption</td>
</tr>
<tr>
<td></td>
<td>Reduced food intake</td>
</tr>
<tr>
<td></td>
<td>Concurrent medications influencing albumin binding, metabolism and excretion of sulphonylureas</td>
</tr>
<tr>
<td></td>
<td>Incorrect use of antidiabetic drug therapies (dose/timing)</td>
</tr>
<tr>
<td></td>
<td>Increased peripheral glucose uptake with exercise</td>
</tr>
</tbody>
</table>
Insulin
Insulin therapies prevent the reduction in circulating insulin occurring as part of the counter-regulatory response. The UKPDS showed that rates of hypoglycaemia were three to four times higher in patients treated with insulin than in those taking SUs. Additionally, patients had a 13-fold higher risk of severe hypoglycaemia requiring emergency treatment when taking insulin compared with OADs.

Other risk factors
Impaired awareness of hypoglycaemia
Impaired awareness of hypoglycaemia is not an uncommon phenomenon in patients with type 2 diabetes and is associated with a substantially increased risk of severe hypoglycaemia when compared to individuals with normal awareness.

Age
Studies have shown that glucose concentration thresholds for induction of the counter-regulatory response decrease with age and that the symptoms of hypoglycaemia may also become less intense. Autonomic symptoms generally occur in younger people at higher blood glucose concentrations than those associated with cognitive impairment, allowing the patient to take corrective action. In older people these symptoms may emerge almost simultaneously, limiting the time available for self-management prior to the onset of incapacitating neuroglycopenia.

Duration of diabetes
Duration of type 2 diabetes is a strong influence on the risk of hypoglycaemia and is linked to increasing age and requirement for insulin therapy. As demonstrated in the UK Hypoglycaemic Study Group trial, for people with type 2 diabetes using insulin for < 2 years, rates of hypoglycaemia were comparable with those using SUs only. However, over time, the prevalence of both mild and severe hypoglycaemia increased.

Co-morbidities
Medical illnesses affecting the counter-regulatory hormone response, e.g. growth hormone deficiency and Addison’s disease, can increase the risk of hypoglycaemia. Hepatic dysfunction, resulting in altered drug metabolism and reduced glucose production, can also influence the likelihood of hypoglycaemia. Alcohol intake acts to suppress endogenous glucose production and impair awareness of hypoglycaemia, even at low concentrations.

Impact of hypoglycaemia
The physical morbidity associated with an episode of hypoglycaemia ranges from the unpleasant autonomic and neuroglycopenic symptoms, through to seizure and coma. Injury to the patient may occur during an episode and in elderly patients hypoglycaemia may also provoke events such as stroke or myocardial infarction. These events can result in patients becoming fearful of experiencing further hypoglycaemic episodes, which can act as a barrier to achieving adequate glycaemic control.

In the ACCORD study, patients with type 2 diabetes were randomised to intensive (target HbA1c < 6.0%) or standard (target HbA1c 7.0–7.9%) glucose-lowering therapy. At 1 year, the proportion of patients experiencing their first occurrence of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes was not significantly different for intensive versus standard therapy. However, a significantly greater proportion of patients in the intensive therapy group died and the incidence of severe hypoglycaemia was substantially higher for intensive versus standard therapy (16.2% versus 5.1%; p<0.001). In the ADVANCE trial, the treatment approach was less aggressive, with stepwise addition of oral agents and eventually basal and mealtime insulins to achieve HbA1c < 6.5%. After a median 5 years of follow-up, intensive therapy achieved a significant reduction in major microvascular and cardiovascular events. Notably, the mortality rates in both treatment groups were low, as were the rates of patients experiencing at least one severe hypoglycaemic event (intensive therapy 2.7% versus standard therapy 1.5%; p<0.001). Following these two studies, it has been suggested that a greater frequency of severe hypoglycaemia may be related to an increase in mortality rate when employing intensive glucose-lowering therapy.

Strategies for minimising the risk of hypoglycaemia
The risk of hypoglycaemia can be substantially reduced through individualised patient education and careful management of pharmacotherapy in-line with the patient’s disease status and co-morbidities.

Patient education
Education should address the prevention, early identification and appropriate treatment (including self-management) of hypoglycaemia (table 3). For example, many patients may be unclear about the influence of meal timing on blood glucose levels and few of those taking SUs are aware of their association with hypoglycaemia. The DOVES study demonstrated that increased diabetes-related knowledge is a key contributor to symptom awareness.

Hypoglycaemia with current pharmacological therapies
Introduction of newer therapies and more individualised and appropriate use of existing agents may help patients maintain improved glucose control while reducing the risk of both hyperglycaemia-related complications and hypoglycaemia. A brief summary of key studies reporting incidences of hypoglycaemia with current treatments is presented below. For conciseness, only results from studies supporting licensed indications of these agents are presented.

Metformin
At 6 years from diagnosis of type 2 diabetes, the UKPDS found that the rates of hypoglycaemia were 0.3% for metformin monotherapy (n=290), compared with 1.2% for SUs (n=1418) and 3.8% for basal insulin therapy (n=1036). In combination
with an SU, metformin (1,500–2,000 mg/day) has been shown to significantly increase the incidence of hypoglycaemia compared with SU monotherapy during 6 months of treatment (11.6% versus 4.2%; p=0.007; n=575). A systematic review of randomised controlled trials has confirmed this finding and also found that the combination of metformin (which reduces insulin resistance) and an SU (which is an insulin secretagogue) is associated with a significantly higher incidence of hypoglycaemia than with metformin alone.34

Thiazolidinediones
A systematic review of randomised controlled trials evaluated the benefits and harms of OADs, including SUs and TZDs.34 The risk of hypoglycaemia was found to be higher for SU monotherapy versus TZD monotherapy. When compared with metformin alone, the combination of metformin plus a TZD (which increases insulin sensitivity) was not associated with an increased risk of hypoglycaemia. However, TZD in combination with SU demonstrated a greater risk of hypoglycaemia than SU monotherapy. A separate meta-analysis has concluded that the addition of a TZD to existing OAD therapy does not significantly alter the incidence of non-severe hypoglycaemia compared with addition of placebo or active control to the OAD therapy.35 However, TZDs are associated with weight gain and oedema.34

Incretin mimetics
Exenatide and liraglutide mimic the actions of endogenous GLP-1, which acts to increase nutrient stimulated insulin secretion, suppress glucagon secretion and slow gastric emptying, as well as increasing satiety.36 In a recent head-to-head, open-label, randomised controlled trial, once-daily liraglutide (n=233) achieved a significantly greater reduction in mean HbA1c than twice-daily exenatide (n=231) over a 26-week period, in patients receiving metformin with or without SUs.37 Both treatments were associated with weight loss, but the incidence of minor hypoglycaemia was lower with liraglutide (26%) than with exenatide (34%; p=0.0131). No patients experienced severe hypoglycaemia with liraglutide, while two patients receiving exenatide plus SU therapy experienced severe hypoglycaemia. The rates of gastrointestinal adverse events were similar for both treatment arms (liraglutide, 45.5%; exenatide, 42.7%).37

A recent meta-analysis concluded that the addition of exenatide to existing OAD therapy demonstrates modest effects on glycaemic control while not significantly increasing the incidence of non-severe hypoglycaemia and demonstrating weight loss.35 However, when compared with controls, exenatide demonstrated high odds ratios for nausea (9.0), vomiting (4.6) and diarrhoea (3.0).35 Two separate randomised, open-label, studies involving patients with suboptimal glycaemic control while receiving metformin, SU or metformin plus SU have evaluated the effects of adding exenatide or insulin glargine to the treatment regimen.38,39 In the first trial, the overall rate of hypoglycaemia was similar for both exenatide and insulin glargine and four patients in each group experienced severe hypoglycaemia.38 The incidence of nocturnal hypoglycaemia was lower with exenatide, whereas the incidence of daytime hypoglycaemia was lower with insulin glargine. In the second study, the incidence of hypoglycaemia with addition of exenatide to metformin was 2.6% versus 17.4% of patients adding insulin glargine to metformin or SU (p=0.01).39 The mean reduction from baseline in HbA1c with exenatide was not significantly different to insulin glargine. However, patients receiving exenatide experienced weight loss, while those receiving insulin glargine experienced weight gain. The proportions of patients suffering nausea or vomiting were higher in the exenatide group.

Dipeptidyl peptidase-4 inhibitors
These agents, also called gliptins, inhibit the key enzyme (DPP-4) responsible for breakdown of endogenous GLP-1.40 The glucose-lowering action of the DPP-4 inhibitors is dependent on the activity of GLP-1, the secretion of which is dependent on nutrients in the intestinal tract. Moreover the insulinotropic action of GLP-1 is glucose dependant, so it may be hypothesised that the action of DPP-4 inhibitors would be associated with a low risk of hypoglycaemia.
In patients with type 2 diabetes inadequately controlled with metformin, sitagliptin was compared with glipizide for 52 weeks. Glycaemic control was similar for both treatments, but hypoglycaemia was significantly more frequent with glipizide (32%) than with sitagliptin (5%; \( p < 0.001 \)). When sitagliptin is combined with glimepiride or glimepiride plus metformin, sitagliptin was associated with hypoglycaemia in 12% of patients compared with 2% of patients receiving placebo. However, when added to existing treatment with pioglitazone, sitagliptin demonstrated no increase in the incidence of hypoglycaemia versus placebo over a 24-week treatment period.

When added to metformin, vildaglaptin demonstrated a similar improvement in HbA1c to glimepiride. However, the incidence of hypoglycaemia was lower with vildaglaptin (1.7%) than with glimepiride (16.2%). No cases of severe hypoglycaemia were reported for patients receiving vildaglaptin, compared with 10 episodes in patients receiving glimepiride. In a separate trial, adding vildaglaptin or pioglitazone to metformin achieved similar reductions in HbA1c. Hypoglycaemia was reported by one patient in the vildaglaptin group and no patients in the pioglitazone group. Body weight remained stable during the 24-week treatment period with vildaglaptin, but progressively increased with pioglitazone. When vildaglaptin and pioglitazone were combined, the incidence of hypoglycaemia remained low and was not different from that with the respective monotherapies.

In patients demonstrating inadequate glycaemic control with metformin monotherapy, the addition of saxagliptin was compared with placebo over a 24-week period. While HbA1c was significantly improved with saxagliptin versus placebo, the incidence of hypoglycaemia was similar for both treatments. In a separate 24-week study, patients taking glyburide and demonstrating suboptimal glycaemic control were randomised to either an increased dose of glyburide or the addition of saxagliptin. The target HbA1c was achieved by a significantly greater proportion of patients receiving combination therapy and the incidence of hypoglycaemia was similar for saxagliptin 2.5 mg plus glyburide (13.3%), saxagliptin 5 mg plus glyburide (14.6%) and glyburide alone (10.1%).

**Long-acting insulin analogues**

Insulin glargine and insulin detemir are long-acting basal insulin analogues that demonstrate a flatter 24-h glucose-lowering profile than NPH insulin, resulting in a more predictable glucose response. In a meta-analysis conducted by the Cochrane Group, rates of total symptomatic and nocturnal symptomatic hypoglycaemia over 24–52 weeks were significantly lower with insulin glargine and insulin detemir than with NPH insulin. However, there were no differences between the insulins for the incidences of severe hypoglycaemia or for reductions in HbA1c. Similar findings were reported for a more recent meta-analysis of these agents.

The Treat to Target study evaluated the addition of insulin glargine or NPH insulin to OADs for a 24-week treatment period. The incidence of symptomatic hypoglycaemia was significantly reduced for insulin glargine versus NPH insulin, whereas the incidence of severe hypoglycaemia was similar (2.5% for insulin glargine versus 1.8% for NPH insulin). In a separate study, symptomatic hypoglycaemia was significantly less frequent with insulin glargine plus OADs than with twice-daily pre-mixed insulins plus OADs, while the incidence of severe hypoglycaemia was comparable. In patients receiving metformin and SU combination therapy, the addition of insulin glargine was associated with a higher (but non-significant) increase in confirmed hypoglycaemic events compared with the addition of rosiglitazone. However, the incidence of confirmed nocturnal hypoglycaemia was significantly higher with insulin glargine than rosiglitazone (\( p < 0.05 \)). Insulin glargine was associated with significantly less weight gain (\( p = 0.02 \)) and oedema (\( p = 0.001 \)) than rosiglitazone.

**Tailoring treatment to the individual**

The propensity of individual therapies to increase the risk of hypoglycaemia must be considered alongside other goals of treatment in patients with type 2 diabetes; namely, maintenance of adequate glycaemic control to prevent development or progression of chronic complications, alterations in cardiovascular risk factors (e.g. weight, lipids) and tolerability. NICE also reinforces the need to offer treatment and care which is tailored to the individual patient’s needs and preferences.

**NICE guidance**

NICE recently published guidance for the use of newer agents for the treatment of type 2 diabetes. Metformin and SUs remain the recommended first-line therapies; however, if HbA1c exceeds 6.5%, an individual patient’s blood glucose control is considered to be inadequate. When the patient is at significant risk of hypoglycaemia, is unable to tolerate metformin or an SU or these agents are contraindicated the guidance recommends adding sitagliptin or vildaglaptin as second-line treatment. Additionally, DPP-4 inhibitors may be considered as third-line therapy when first-line metformin and second-line SU fail to maintain adequate blood glucose control (HbA1c ≥ 7.5%) and insulin therapy is unacceptable or inappropriate. NICE also suggests that DPP-4 inhibitors can be considered instead of TZDs in patients for whom further weight gain may be clinically unacceptable, TZDs are contraindicated, or previous treatment with a TZD was associated with a poor response or poor tolerability. In all instances, NICE states that treatment with sitagliptin or vildaglaptin should only be continued if a reduction in HbA1c by ≥ 0.5% over a 6-month period is achieved.

In this guidance, exenatide is proposed as a third-line therapy only, for patients receiving combination metformin and SU therapy who are not achieving adequate blood glucose control and who have a BMI ≥ 35 kg/m² and specific medical or psychological problems associated with high body weight; or BMI < 35 kg/m², insulin therapy is not feasible and weight loss would be beneficial. NICE states that exenatide therapy should achieve a reduction in HbA1c of ≥ 1% and a decrease in body weight of ≥ 3% over a 6-month period if treatment is to be continued.
In the later stages of type 2 diabetes, NICE recommends that the long-acting insulin analogues be used as alternatives to NPH insulin. This recommendation is based on patients who receive assistance for their insulin injection, in those that would otherwise need twice-daily basal insulin injections or in those for whom hypoglycaemia restricts their lifestyle. In line with the growing recognition of hypoglycaemia as a significant issue in the treatment of type 2 diabetes, the guidance also specifies that when patients start using insulin therapy a structured programme of education, telephone support, self-monitoring, management of hypoglycaemia and healthcare professional support should be provided.

Conclusions

Hypoglycaemia in patients with type 2 diabetes is an important issue, in terms of potential morbidity and mortality, as well as its impact on achieving adequate glycaemic control. This is likely to become a greater problem as the type 2 diabetes population grows and insulin use becomes more frequent. Patient education, coupled with appropriate, individualised treatment strategies could achieve a reduction in the incidence of hypoglycaemic events. The basal insulin analogues and novel agents modulating the incretin system may have a key role to play in this approach.

Conflicts of interest

The author has received honoraria from Bristol-Myers Squibb and has been involved in advisory boards for Bristol-Myers Squibb, AstraZeneca, Lilly, Merck Sharp & Dohme, NovoNordisk and Novartis.

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