Prevention and management of hypoglycaemia in diabetes

The benefits of strict glycaemic control in delaying the onset and progression of micro and macrovascular complications in diabetes are undisputed[1,2] but determining appropriate HbA1c targets remains controversial. This is a particular dilemma when treating patients who have coronary heart disease, particularly the very elderly, many of whom are frail and have several comorbid medical disorders.[3]

Dr RM Noh, Clinical Research Fellow, Department of Diabetes, Royal Infirmary of Edinburgh,
Dr Brian M Frier, Consultant Physician and Honorary Professor of Diabetes, Department of Diabetes, Royal Infirmary of Edinburgh,
***email: brian.frier@luht.scot.nhs.uk**

The principal problem associated with strict glycaemic control and intensified therapy in management of diabetes is the heightened risk of hypoglycaemia, which is underestimated in everyday clinical practice. Hypoglycaemia is a very common side-effect of insulin, but is also associated with secretagogues such as sulfonylureas and glinides, and in certain circumstances (such as intercurrent illness with anorexia and prolonged fasting) can be precipitated by any anti-diabetes drug. Hypoglycaemia is frightening, dangerous and disruptive to everyday life. It can cause significant morbidity and is a major barrier to achieving and maintaining optimal long-term control.

Definition

A valuable and clinically relevant definition of hypoglycaemia is based on the ability of an individual to self-treat low blood glucose. Therefore, mild hypoglycaemia is an episode where the affected person is able to self-treat, and severe hypoglycaemia is defined by an event that requires external assistance.[4]

Frequency

The risk of mild and severe hypoglycaemia is much higher overall in individuals with type 1 diabetes mellitus, but the absolute number of people with insulin-treated type 2 diabetes mellitus is very much greater, so hypoglycaemia in type 2 diabetes is a much larger clinical problem than is generally appreciated.

In populations with type 1 diabetes, the annual prevalence of severe hypoglycaemia is 30%, and an incidence varying from one to three episodes per patient per year, with the highest rate occurring in people with type 1 diabetes >15 years.[5] Thus risk of severe hypoglycaemia increases with the duration of the disorder and is greatest at the extremes of age (the very young and very old).[6] The average frequency of mild hypoglycaemia in type 1 diabetes is around two episodes per patient per week.[7]

Many healthcare professionals believe that people with type 2 diabetes have a low risk of developing hypoglycaemia, a perception that may have been reinforced by the low rates of hypoglycaemia reported in many clinical trials, which bear little resemblance to everyday life. Hypoglycaemia is rare in diet-controlled type 2 diabetes but in people treated with sulfonylureas is much higher than recognised. In well-controlled patients in the UK Hypoglycaemia Group Study, the annual prevalence of severe hypoglycaemia was 7% in those receiving a sulfonylurea, which was equivalent to the frequency observed in those who had been taking multiple injections of insulin for up to two years. In those with type 2 diabetes who had been treated with insulin for more than five years the prevalence of severe hypoglycaemia was higher at 25% —similar to that observed in people with type 1 diabetes of short duration (<5 years)—confirming that in insulin-treated type 2 diabetes the risk of severe hypoglycaemia increases with duration of insulin therapy.

The Diabetes Audit Registry in Tayside/Medicines Monitoring (DARTS/MEMO) group prospectively examined hypoglycaemic events requiring emergency medical assistance or hospital admission over a period of one year;

Table 1: Commonest symptoms of hypoglycaemia in adults with insulin-treated diabetes. In older people, neuroglycopenic symptoms may predominate and neurological symptoms are also present.

Autonomic/ Sympatho-adrenal	Neuroglycopenic	Neurological (older people)	Non-specific
Tremor	Incoordination	Unsteadiness	Headache
Hunger	Speech difficulty	Poor coordination	Malaise
Palpitations	Mood changes/ odd behaviour	Blurred vision	
Sweating	Confusion	Double vision	
	Drowsiness	Slurred speech	

7.3% of insulin-treated patients with type 2 diabetes required emergency treatment, compared with 0.8% of patients treated with sulfonylureas.[8] The incidences of severe hypoglycaemia were 11.8 and 0.9 events per 100 patient years respectively. However, this represents the tip of the iceberg as only 10% of episodes of severe hypoglycaemia in type 1 diabetes and 30% in insulin-treated type 2 diabetes are treated by the emergency services—most episodes are treated at home.[9] Many severe events are not reported to GPs, either by the patients[10] or by the emergency services.

Clinical features

The stress of acute hypoglycaemia provokes the secretion of several counter regulatory hormones and stimulates the autonomic nervous system as a measure to preserve the supply of glucose to the brain. This generates typical autonomic and neuroglycopenic symptoms that are associated with hypoglycaemia (Table 1).[11] These vary considerably between individuals, change with time and are modified by age; in older people autonomic responses are less prominent, while neuroglycopenic symptoms predominate.[12] Awareness of the onset of hypoglycaemia is reduced, which restricts the time available to treat it and may make older people more susceptible to develop severe cases. In addition, older people experience neurological symptoms such as visual disturbance, incoordination and ataxia, so that hypoglycaemia in the elderly may be confused with stroke, transient ischaemic attacks or early dementia.[13] Many surveys have shown that older people, and their relatives, have little knowledge of the symptoms of hypoglycaemia, particularly in relation to oral anti-diabetes medications.[14]

Causes and risk factors

Hypoglycaemia is caused by a mismatch between insulin and the ingestion of carbohydrate in food or the production of glucose by the body. The common causes are therefore too much insulin (or sulfonylurea), delayed food or unexpected strenuous exercise. However, a number of risk factors are recognised to increase susceptibility to develop hypoglycaemia, including the duration of diabetes, increasing age, the co-existence of comorbidities such as renal impairment, sleep, and a previous history of severe hypoglycaemia. In older people with type 2 diabetes, polypharmacy may be a serious problem as sulfonylureas can interact with several other drugs and the risk of hypoglycaemia rises with renal and hepatic failure (Table 2).[15,16] Long-acting sulfonylureas such as glibenclamide, are not recommended for use in elderly patients, as they frequently induce prolonged severe hypoglycaemia.[17] The syndrome of impaired awareness of hypoglycaemia (IAH) is well recognised as a complication of insulin therapy in type 1 diabetes and although much less common in people with insulin-treated type 2 diabetes, it also presents an important risk factor.[18]

Prevention and management of hypoglycaemia in the older person

Education

Because hypoglycaemia is such a common problem in the treatment of type 1 diabetes, methods of limiting hypoglycaemia have been directed at this group, particularly for those who have developed impaired awareness of hypoglycaemia. Structured educational programmes have been devised to teach affected patients how to identify

Table 2: Drug interactions that modify the hypoglycaemic effect of sulfonylureas

Example of Drugs	Mechanism of potentiation of hypoglycaemic effects of sulfonylureas
Warfarin, salicylates, fibrates, sulphonamides	Decrease plasma protein binding
Warfarin, Monoamine oxidase inhibitors	Decrease hepatic metabolism
Non-steroidal anti inflammatory drugs	Increase insulin secretion
Salicylates, probenecid, allopurinol	Decrease renal excretion

their residual warning symptoms and when to anticipate a fall in blood glucose. Lower rates of hypoglycaemia can be achieved without compromising glycaemic control.[19] However, these programmes are labour-intensive and require the specialised input of a psychologist.

Much more fundamental is to ensure that people with type 2 diabetes, and their relatives, are adequately informed about the potential risks of hypoglycaemia with treatment such as sulfonylureas and insulin, how to take precautions to avoid a fall in blood glucose and how to treat hypoglycaemia at an early stage. Simple practical information about hypoglycaemia and its prevention is often provided at the time of commencing treatment for type 2 diabetes, or when insulin treatment is started. Unfortunately, this is usually accompanied by a plethora of other necessary information about management of type 2 diabetes and advice about hypoglycaemia is seldom reinforced. This is compounded by the fact that more than one fifth of older patients who have type 2 diabetes have co-existing short-term memory loss or other cognitive impairment.[14] Few educational programmes in type 2 diabetes focus on how to limit hypoglycaemia, and are targeted at people with newly diagnosed type 2 diabetes when hypoglycaemia is uncommon. It should be emphasised as being a potential side-effect of sulfonylureas and insulin, and a group approach to education may disadvantage individual patients who need "one to one" tuition. This puts pressure on limited clinical resources and their knowledge may have to be reviewed at intervals. Involving carers and family members in knowing how to identify hypoglycaemia and quickly instigate effective treatment is vital to the prevention of severe hypoglycaemia. Hypoglycaemia is seldom discussed during routine clinical review of people with type 2 diabetes and some useful questions to ask during a subsequent consultation are listed in Table 3.[20]

Self-blood glucose monitoring (SBGM)

SBGM should be routine practice for all insulin-treated people with diabetes. However, to limit costs, routine monitoring is often discouraged or refused in people with type 2 diabetes treated with oral therapy, even though current NICE guidelines suggest the use of SBGM in people using sulfonylurea therapy, especially where hypoglycaemia is a concern. This may be particularly important in relation to safe driving practice. The interpretation of blood glucose results should ideally be assisted by a healthcare professional. The use of Continuous Blood Glucose Monitoring (CGM), with devices incorporating a "hypoglycaemia alarm" is attractive but is unproven clinically and the cost is currently prohibitive.[21]

Lifestyle considerations

Alcohol increases the risk of hypoglycaemia through inhibition of counter-regulatory responses, and by impairing awareness of hypoglycaemia. This can occur when either sulfonylureas or insulin are used. Patients taking these therapies should be advised to check their blood glucose regularly and to consume carbohydrates before, or along with the consumption of alcohol.[22] Exercise is a valuable part of the management of type 2 diabetes and should be encouraged, but older people taking insulin (and also SUs) require advice about the need to consume additional carbohydrate if exercise is relatively strenuous (such as gardening or dancing), and to monitor their blood glucose appropriately.

Pharmacological strategies

An important part of avoiding hypoglycaemia is the appropriate selection of therapies. Maintaining glycaemic control while minimising hypoglycaemia may be difficult

JANUVIA®▼sitagliptin

PRESCRIBING INFORMATION

Refer to Summary of Product Characteristics (SPC) before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to MSD (tel: 01992 467272).

PRESENTATION

25 mg film-coated tablet containing 25 mg of sitagliptin

50 mg film-coated tablet containing 50 mg of sitagliptin

100 mg film-coated tablet containing 100 mg of sitagliptin.

USES

For adult patients with type 2 diabetes mellitus 'Januvia' is indicated to improve glycaemic control:

as monotherapy

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance

as **dual oral therapy** in combination with

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contra-indications or intolerance
- a PPARγ agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control

as **triple oral therapy** in combination with

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Januvia is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin do not provide adequate glycaemic control.

DOSAGE AND ADMINISTRATION

One 100 mg tablet once daily, with or without food. When sitagliptin is used in combination with metformin and/or a PPARγ agonist, maintain the dosage of metformin and/or PPARγ agonist, and administer sitagliptin concomitantly. When used in combination with a sulphonylurea or with insulin, consider a lower dose of sulphonylurea or insulin, to reduce risk of hypoglycaemia. If a dose of Januvia is missed, take as soon as the patient remembers. Do not take a double dose on the same day.

Renal impairment: when considering use in combination with other anti-diabetic products, check conditions for use in patients with renal impairment. No dosage adjustment required for mild renal impairment (creatinine clearance [CrCl] ≥50 ml/min). For patients with moderate renal impairment (CrCl ≥30 to <50 mL/min), the dose of 'Januvia' is 50 mg once daily. For patients with severe renal impairment (CrCl <30 mL/min) or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis, the dose of 'Januvia' is 25 mg once daily. 'Januvia' may be administered without regard to the timing of dialysis. Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of 'Januvia' and periodically thereafter. Hepatic impairment: no dosage adjustment necessary for patients with mild to moderate hepatic impairment. Januvia has not been studied in patients with severe hepatic impairment. Elderly: no dosage adjustment necessary. Exercise care in patients ≥ 75 years of age as there are limited safety data in this group. Children: not recommended in children below 18 years of age.

CONTRA-INDICATIONS

Hypersensitivity to active substance or excipients.

PRECAUTIONS

General: do not use in patients with type 1 diabetes or for diabetic ketoacidosis.

Pancreatitis: Post-marketing experience - spontaneously reported adverse reactions of acute pancreatitis. Inform patients of the symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin, but very rare cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, 'Januvia' and other potentially suspect medicinal products should be discontinued.

Hypoglycaemia when used with other anti-hyperglycaemic agents: Rates of hypoglycaemia reported with sitagliptin were generally similar to rates in patients taking placebo. When sitagliptin was added to a sulphonylurea or to insulin, the incidence of hypoglycaemia was increased over that of placebo; therefore consider a lower dose of sulphonylurea or insulin to reduce the risk of hypoglycaemia. Renal impairment: 'Januvia' is renally excreted. To achieve plasma concentrations of 'Januvia' similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal impairment, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (see section 'Dosage and administration' above and section 4.2 and 5.2 of the SmPC). Hypersensitivity reactions: Serious hypersensitivity reactions have been reported, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset occurred within the first 3 months after initiation of treatment with some reports occurring after the first dose. If suspected, discontinue 'Januvia', assess for other potential causes and institute alternative treatment for diabetes.

Drug interactions

Low risk of clinically meaningful interactions with metformin and ciclosporin. Meaningful interactions would not be expected with other p-glycoprotein inhibitors. The primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8.

Digoxin: sitagliptin had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein in vivo. No dosage adjustment of digoxin is recommended, but monitor patients at risk of digoxin toxicity if the two are used together.

Pregnancy and lactation: Do not use during pregnancy or breast-feeding.

SIDE EFFECTS

Refer to SPC for complete information on side effects

Sitagliptin monotherapy: *Common (≥ 1/100 to <1/10)*: upper respiratory tract infection†, nasopharyngitis†, osteoarthritis†, pain in extremity† hypoglycaemia‡, headache; *Uncommon (≥ 1/1,000 to <1/100)*: dizziness, constipation. Combination with metformin: *Common (≥ 1/100 to <1/10)*: hypoglycaemia‡, nausea, flatulence, vomiting; *Uncommon (≥ 1/1,000 to <1/100)*: somnolence, constipation, upper abdominal pain, diarrhoea, blood glucose decreased. Combination with a sulphonylurea: *Common (≥ 1/100 to <1/10)*: hypoglycaemia‡. Combination with metformin and a sulphonylurea: *Very common (≥ 1/10)*: hypoglycaemia‡; *Common (≥ 1/100 to <1/10)*: constipation. Combination with a PPARγ agonist (pioglitazone): *Common (≥ 1/100 to <1/10)*: hypoglycaemia‡, flatulence, peripheral oedema, blood glucose decreased. Combination with a PPARγ agonist and metformin: *Common (≥ 1/100 to <1/10)*: upper respiratory tract infection†, headache, diarrhoea, vomiting, hypoglycaemia‡, peripheral oedema, cough§; *Uncommon (≥ 1/1,000 to <1/100)*: fungal skin infection†. Combination with insulin with/without metformin: *Common (≥ 1/100 to <1/10)*: headache, hypoglycaemia‡, influenza; *Uncommon (≥ 1/1,000 to <1/100)*: dry mouth, constipation.

Adverse events with sitagliptin alone in clinical studies, or during post-approval use alone and/or with other diabetes medicines where frequency is not known: hypersensitivity reactions including anaphylactic responses (see section 4.4)‖,‡, interstitial lung disease‡, vomiting‡, acute pancreatitis‡ fatal and non-fatal haemorrhagic and necrotizing pancreatitis‡,‖, angioedema‡,‖, rash‡,‖, urticaria‡,‖, cutaneous vasculitis‡,‖, exfoliative skin conditions‡,‖ including Stevens-Johnson syndrome‡,‖, arthralgia‡, myalgia‡, impaired renal function‡, acute renal failure‡.

† Based on incidence regardless of causal relationship.

‡ Adverse reactions were identified through postmarketing surveillance.

§ 54-week time point.

‖ See precautions.

PACKAGE QUANTITIES AND BASIC NHS COST

28 Tablets: £33.26

Marketing Authorisation Number

EU/1/07/383/002 – **Januvia** 25 mg tablets

EU/1/07/383/008 – **Januvia** 50 mg tablets

EU/1/07/383/014 – **Januvia** 100 mg tablets

Marketing Authorisation Holder

Merck Sharp & Dohme Limited

Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review of prescribing information: March 2012**

PI.JAN.ALL.12.UK.3615

References:

1. Data on file,
2. IMS Health, NPA™ Monthly, TRxs, October 2006 - November 2011
3. Ferreira JCA. et al. Efficacy and Safety of Sitagliptin versus Glipizide in Patients with Type 2 Diabetes and Moderate to Severe Chronic Renal Insufficiency, PN 063, Poster, 2011 EASD.
4. Ferreira JCA. et al. Efficacy and Safety of Sitagliptin vs. Glipizide in Patients with Type 2 Diabetes Mellitus and End-stage Renal Disease on Dialysis: A 54-week Randomised Trial, PN 073, Poster, 2011 EASD.
5. Chan JCN et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes, Obesity and Metabolism, 10; 545-555, 2008.

Once-daily Januvia® ▼ (sitagliptin)

MSD

Table 3: Useful questions for clinic consultations to ascertain the level of knowledge of hypoglycaemia[20]

What does the patient know and believe about hypos?
- What does the term 'hypo' or hypoglycaemia mean to you?
- What does having a hypo feel like?
- What effect do you think hypos have on you
  - while driving??
  - when at work?
  - on your mood?

How does the patient experience hypos?
- What symptoms do you experience when you think you are having a hypo?
- When you have a hypo, how long does it take for you to return to normal?
- Are there any lingering effects after the hypo?
- How often do you find yourself having a blood sugar lower than 4mmol/L and not having symptoms of a hypo?

How often is the patient experiencing mild (self-treated) hypoglycaemia?
- In the last six months, how often have you had to treat a hypo yourself? Choose the following
  - Never
  - Once a month
  - Two to three times a month
  - Once a week

How often is the patient experiencing severe hypoglycaemia?
- Have you had a hypo which required somebody to give you treatment because you could not do this yourself?
- If so, how often has this happened?
  - once a year
  - two to five times a year
  - more than five times a year
- Have you had a severe episode in the last year?

Exploring quality of life with hypoglycaemia
- What has been the worst experience of you having a hypo?
- How does hypoglycaemia affect your everyday life?
- Has a severe hypo ever caused you to have an accident or be injured?
- Have you ever been admitted to hospital because of a hypo?

Exploring treatment effectiveness of hypos
- How do you treat your hypos?
- What do you find works best for you in treating your hypos?

Exploring prevention strategies of hypoglycaemia
- What do you think causes your hypos?
- What do you think could help you have fewer hypos?

to achieve, and treatment and glycaemic targets should be tailored to individual needs. In the frail elderly or those with cardiovascular comorbidities, hypoglycaemia should be avoided completely. The debate as to what the target HbA1c value should be continues, but a large retrospective cohort study showed a U-shaped curve for mortality of patients with type 2 diabetes, with the lowest mortality rate being associated with a HbA1c of 7.5%. In the frail elderly or those with cardiovascular comorbidities, this target seems very sensible.[23] The speed of achieving this target is also important; an aggressive approach to intensification of treatment using

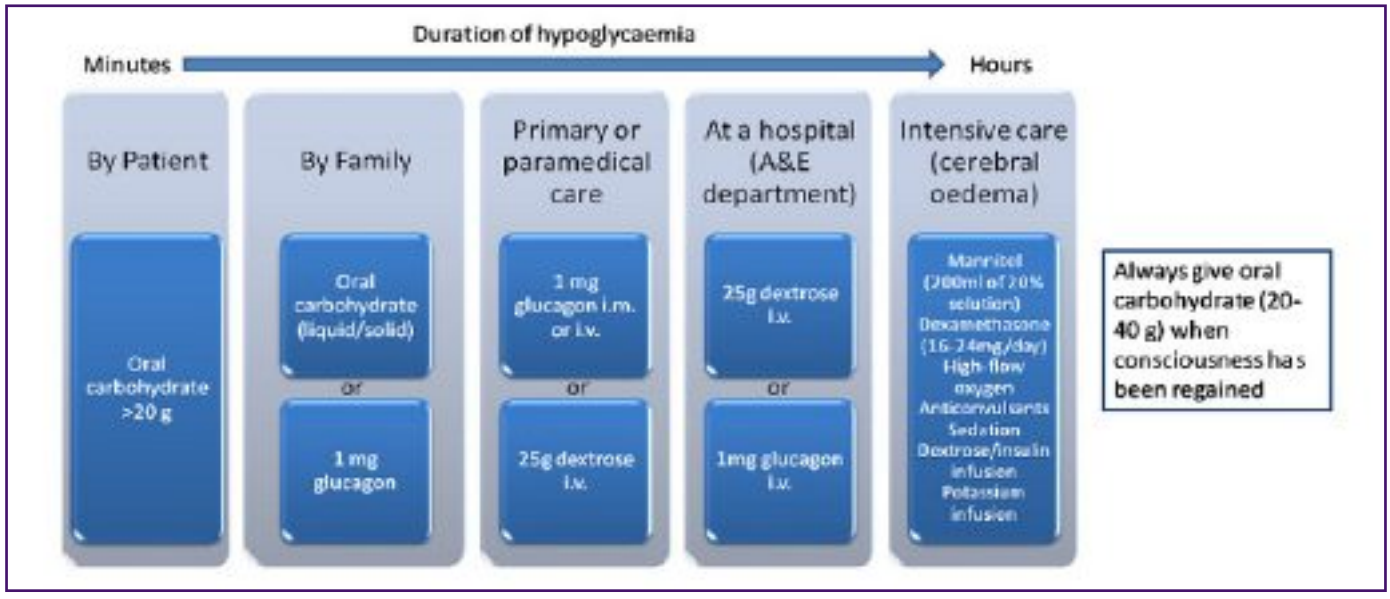

Figure 1: Management of hypoglycaemia. Adapted from the Association of British Clinical Diabetologists' Guidelines[24]

multiple drugs without adequate education is potentially hazardous. Metformin is the first-line oral therapy and although the risk of hypoglycaemia with metformin is low, it can still occur in the context of prolonged fasting or intercurrent illness.

NICE guidance on intensification of therapy after metformin states that where there are specific concerns about hypoglycaemia, agents such as a dipeptidyl-peptidase-4 (DPP-4) inhibitor (gliptins), or pioglitazone (Actos), may be used instead of sulfonylurea. These agents provide similar efficacy for glycaemic control with minimal hypoglycaemia.[21] Studies evaluating the effect of gliptins on long-term complications of diabetes are still lacking. When sulfonylureas are used in elderly patients, it is prudent to use short-acting agents such as gliclazide or glipizide (Glucotrol), and to up-titrate slowly. In those requiring insulin, the use of long-acting basal insulin added to oral agents is associated with similar glycaemic control to insulin monotherapy, with no difference in hypoglycaemia rates.

The hypoglycaemia emergency—when to admit to hospital?

Figure 1 shows an algorithm adapted from the Joint Diabetes Societies guidelines in treating hypoglycaemia.[24] Hypoglycaemia which causes loss of consciousness and/or seizure will usually require admission to hospital. When dealing with severe hypoglycaemia, the duration of hypoglycaemia is the main determinant of the level of care required.[25] In the elderly, many considerations are relevant to the decision to seek admission. Frail patients with cognitive impairment or poor social support require more frequent monitoring. Patients with renal impairment on sulfonylureas, and those receiving polypharmacy (beta-blockers, ACE-inhibitors) are more prone to prolonged life-threatening hypoglycaemia, and require more support. It is important to remember that hypoglycaemia can provoke major vascular events such as stroke and myocardial infarction. Many medical practitioners do not ascertain whether hypoglycaemia may have played a causative role in these events, perhaps because of unfamiliarity with the age-related neurological manifestations of hypoglycaemia. Over and above the decision to admit the patient to hospital, it is imperative to explore what may have caused the acute episode of hypoglycaemia. Any relevant change in circumstance (eg. a significant change to caloric intake because of intercurrent illness or an inability to swallow), should be considered and a change in the dose of medication or insulin instituted to avoid repetition. When hypoglycaemia is severe or recurrent, it may be prudent to liaise with a specialist diabetes team.

Conclusion

In the older individual, hypoglycaemia can cause significant morbidity. Ageing modifies the responses to hypoglycaemia, and effective self-treatment may be compromised by

cognitive dysfunction. Fear of hypoglycaemia is a major barrier of good glycaemic control and leads to poorer quality of life. As ever in diabetes management, prevention is better than cure and minimising hypoglycaemia requires addressing educational provision, lifestyle factors and tailoring pharmacological therapy to the individual.

Conflict of interest: none declared

References

1. The Diabetes Control and Complication Trial Research Group. Hypoglycemia in the Diabetes Control and Complication Trial. *Diabetes* 1997; **46**: 271–86
2. United Kingdom Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS33). *Lancet* 1998; **352**: 837–53
3. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive Glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52**: 2288–98
4. American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005; **28**: 1245–49
5. United Kingdom Hypoglycaemia Study Group. Risk of hypoglycaemia in types1 and 2 diabetes: effect of treatment modality and their duration. *Diabetologia* 2007; **50**: 1140–47
6. Pramming S, Thorsteinsson B, Bendtson I, et al. Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabet Med* 1991;**8**: 217–22
7. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. *Diabetes Metab Res Rev* 2004; **20**: 479–86
8. Leese GP, Wang J, Broomhall J, et al for the DARTS/MEMO collaboration. Frequency of severe hypoglycemia requiring emergency department treatment in type 1 and type 2 diabetes. A population-based study health service resource use. *Diabetes Care* 2003; **26**: 1176–80
9. Donnelly LA, Morris AD, Frier BM, et al. for the DARTS/MEMO collaboration. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabetic Medicine* 2005; **22**: 749–55
10. Leiter LA, Yale JF, Chiasson JL et al. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes* 2005; **29**: 186–92
11. Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory analysis. *Diabetologia* 1993; **36**: 771–77
12. Matyka KA, Evans M, Lomas J et al. Altered hierarchy of protective responses against severe hypoglycemia in normal ageing in healthy men. *Diabetes Care* 1997; **20**: 135–41
13. Jaap AJ, Jones GC, Frier BM, et al. Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. *Diabet Med* 1998;**15**: 398–401
14. Hewitt J, Smeeth L. Fletcher AE, et al. Self management and patient understanding of diabetes in the older person. *Diabet Med* 2011; 117–22
15. Campbell IW, Chalmers J, Herlihy OM. Sulphonylurea-induced hypoglycaemia in elderly people with diabetes. *Practical Diabetes* 1994; **11**:102–3
16. Harrigan RA, Nathan MS, Beattie P. Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity and treatment. *Annals of Emergency Medicine* 2001;**38**:68-78
17. Gangji AS, Cuckierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events. *Diabetes Care* 2007; **30**: 389–94
18. Frier BM. Impaired hypoglycaemia awareness. In: Frier BM, Fisher M editors. Hypoglycaemia in Clinical diabetes. 2nd edition. John Wiley & Sons. Chichester 2007. p 141-70
19. Cox DJ, Kovatchev B, Koev D, et al. Hypoglycemia anticipation, awareness and treatment training (HAAT) reduces the occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. *Int J Behav Med* 2004; **11**: 212–18
20. Craddock S, Frier BM. Determining the risk of hypoglycaemia in people with type 2 diabetes: an approach for clinical practice. British Journal of Diabetes & Vascular Disease 2010;10: 44. Online version available from http://dvd.sagepub.com/content/10/1/44
21. National Institute of Clinical Excellence. Guidelines for Management of Diabetes.Available from:http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf. Last accessed March 2011.
22) Burge MR, Zeise T-M, Sobhy TA, et al. Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care* 1999; **22**: 2037–43
23. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; **375**: 481–89
24. The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus- March 2010. available online from: http://www.diabetes.nhs.uk/our_publications/reports_and_guidance/emergency_and_inpatient/. Last accessed: August 2011.
25. MacCuish AC. Treatment of Hypoglycaemia. In: Frier BM, Fisher BM, eds. Hypoglycaemia and Diabetes: Clinical and Physiological aspects. Edward Arnold London 1993, p 212-221.