Clinical Practice Guidelines

Hypoglycemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- It is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues.
- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose (BG) level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly.
- It is important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

Introduction

Drug-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. Frequency and severity of hypoglycemia negatively impact on quality of life (1) and promote fear of future hypoglycemia (2,3). This fear is associated with reduced self-care and poor glucose control (4–6). As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues (see Pharmacotherapy in Type 1 Diabetes, p. S56, and Pharmacologic Management of Type 2 Diabetes, p. S61, for further discussion of drug-induced hypoglycemia).

Definition of Hypoglycemia

Hypoglycemia is defined by 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue); and 3) symptoms responding to the administration of carbohydrate (7). The severity of hypoglycemia is defined by clinical manifestations (Table 2).

Complications of Severe Hypoglycemia

Short-term risks of hypoglycemia include the dangerous situations that can arise while an individual is hypoglycemic, whether at home or at work (e.g. driving, operating machinery). In addition, prolonged coma is sometimes associated with transient neurological symptoms, such as paresis, convulsions and encephalopathy. The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae, such as hemiparesis and pontine dysfunction. The latter are rare and have been reported only in case studies.

Recurrent hypoglycemia may impair the individual's ability to sense subsequent hypoglycemia (8,9). The neurohormonal counterregulatory responses to hypoglycemia may become blunted; however, this is potentially reversible (see Pharmacotherapy in Type 1 Diabetes, p. S56).

Retrospective studies have suggested a link between frequent severe hypoglycemia (≥5 episodes since diagnosis) and a decrease in intellectual performance. These changes were small but, depending on an individual's occupation, could be clinically meaningful. Prospective studies in type 1 diabetes have not found an association between intensive insulin therapy and cognitive function (10–12). A meta-analysis concluded that lowered cognitive performance in people with type 1 diabetes appeared to be associated with the presence of microvascular complications but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control (13). Unlike patients with type 1 diabetes, those with type 2 diabetes and previous severe hypoglycemia requiring presentation to the hospital have increased risk of subsequent dementia (14).

In patients with type 2 diabetes and established, or very high risk for, cardiovascular disease, symptomatic hypoglycemia (<2.8 mmol/L) is associated with increased mortality (15). The mechanism for this increase is not certain; however, acute hypoglycemia is proinflammatory (16) and may affect cardiac conduction (depolarization, QT prolongation). This effect, however, may be related to sympathetic tone rather than glucose per se (17,18).

Table 1
Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Table 2
Severity of hypoglycemia

Mild: Autonomic symptoms are present. The individual is able to self-treat.
Moderate: Autonomic and neuroglycopenic symptoms are present.
The individual is able to self-treat.
Severe: Individual requires assistance of another person.
Unconsciousness may occur. PG is typically <2.8 mmol/L.

PG, plasma glucose.

The major risk factors for severe hypoglycemia in patients with type 1 diabetes include prior episode of severe hypoglycemia (19–21), current low glycated hemoglobin (A1C) (<6.0%) (20,22–24), hypoglycemia unawareness (25), long duration of diabetes (23,26), autonomic neuropathy (27), adolescence (28) and preschool-age children unable to detect and/or treat mild hypoglycemia on their own. Risk factors for hypoglycemia in patients with type 2 diabetes include advancing age (29), severe cognitive impairment (30), poor health literacy (31), food insecurity (32), increased A1C (29,33), hypoglycemia unawareness (34), duration of insulin therapy, renal impairment and neuropathy (33). In patients with type 2 diabetes and established cardiovascular disease (CVD) or age >54 years and 2 CVD risk factors, the risk of hypoglycemia is also increased by female gender (29). Patients at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through self-monitoring of blood glucose (BG) and taking appropriate precautions prior to the activity, and documenting BG readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk. Risk factors for severe hypoglycemia are listed in Table 3.

Treatment of Hypoglycemia

The goals of treatment for hypoglycemia are to detect and treat a low BG level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid over-treatment since this can result in rebound hyperglycemia and weight gain.

Evidence suggests that 15 g glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (Table 4) (35–39). This has not been well studied in patients with gastropathy. A 20 g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (36,37). Other choices, such as milk and orange juice, are slower to increase BG levels and provide symptom relief (36,37). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (35,40). Patients taking an alpha-

Table 3
Risk factors for severe hypoglycemia

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of insulin therapy
- Autonomic neuropathy
- Low economic status
- Food insecurity
- Low health literacy
- Cognitive impairment
- Adolescence
- Preschool-age children unable to detect and/or treat mild hypoglycemia on their own

A1C, glycated hemoglobin.

Table 4
Examples of 15 g carbohydrate for treatment of mild to moderate hypoglycemia

- 15 g glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 LifeSavers (1 = 2.5 g carbohydrate)
- 15 mL (1 tablespoon) of honey

glucosidase inhibitor (acarbose) must use glucose (dextrose) tablets (41) or, if unavailable, milk or honey to treat hypoglycemia. Glucagon 1 mg given subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 to 12.0 mmol/L) within 60 minutes (42). The effect is impaired in individuals who have consumed more than 2 standard alcoholic drinks in the previous few hours or in those who have advanced hepatic disease (43,44).

Hypoglycemia and driving

Individuals with diabetes are a heterogenous group, and the risk of motor vehicle accidents and driving violations may be only slightly increased or markedly increased (relative risk [RR] 1.04 to 3.24) (45). Factors include age, level of A1C, degree of hypoglycemic awareness, miles driven, presence of complications and many others.

Advances in treatment, medical technology and self-monitoring have increased the ability of patients with diabetes to control their disease and operate a motor vehicle safely. The fitness of these patients to drive must be assessed on an individual basis. Individuals with diabetes should be encouraged to take an active role in assessing their ability to drive. Patients should have information concerning avoidance, recognition and appropriate therapeutic

RECOMMENDATIONS

1. Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels [Grade B, Level 2 (35)]. Patients should retest BG in 15 minutes and re-treat with another 15 g carbohydrate if the BG level remains <4.0 mmol/L [Grade D, Consensus]. *Note:* This does not apply to children. See Type 1 Diabetes in Children and Adolescents, p. S153, and Type 2 Diabetes in Children and Adolescents, p. S163, for treatment options in children.

2. Severe hypoglycemia in a conscious person should be treated by oral ingestion of 20 g carbohydrate, preferably as glucose tablets or equivalent. BG should be retested in 15 minutes and then re-treated with another 15 g glucose if the BG level remains <4.0 mmol/L [Grade D, Consensus].

3. Severe hypoglycemia in an unconscious individual
   a. With no IV access: 1 mg glucagon should be given subcutaneously or intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the diabetes healthcare team as soon as possible [Grade D, Consensus].
   b. With IV access: 10–25 g (20–50 cc of D50W) of glucose should be given intravenously over 1–3 minutes [Grade D, Consensus].

4. For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection [Grade D, Consensus].

5. Once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed [Grade D, Consensus].

6. Patients receiving antihyperglycemic agents that may cause hypoglycemia should be counselled about strategies for prevention, recognition and treatment of hypoglycemia related to driving and be made aware of provincial driving regulations [Grade D, Consensus].

Abbreviation:
BG, blood glucose.

intervention for hypoglycemia. Drivers with diabetes should be assessed for possible complications, including eye disease, neuropathy (autonomic, sensory, motor), renal disease and cardiovascular disease. In general, a patient is considered fit to drive if he or she is medically fit, is knowledgeable about controlling BG levels and is able to avoid severe hypoglycemic episodes.

Other Relevant Guidelines

Targets for Glycemic Control, p. S31
Monitoring Glycemic Control, p. S35
Pharmacotherapy in Type 1 Diabetes, p. S56
Pharmacologic Management of Type 2 Diabetes, p. S61
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S184

Related Website

Begg IS, Yale J-F, Houlden RL, et al. Canadian Diabetes Association's clinical practice guidelines for diabetes and private and commercial driving. Can J Diabetes. 2003;27:128–140. Available at: http://www.diabetes.ca/files/DrivingGuidelinesBeggJune03.pdf. Accessed April 30, 2012.

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