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Review Article

Drug-induced hypoglycemia

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Abstract

Hypoglycemia is a clinical syndrome with diverse causes in which low levels of plasma glucose eventually lead to neuroglycopenia. Hypoglycemia is the most common endocrine emergency faced by practicing physicians. Though hypoglycemia is a very common medical problem both in adults and children seeking medical help, most of it is iatrogenic. Treatment with oral hypoglycemic agents, alone or in combination, and/or insulin is an ongoing threat for diabetic patients and still accounts for the majority of cases of hypoglycemia. Numerous other drugs have been reported to induce hypoglycemia, sometimes in seemingly healthy individuals in whom it may masquerade as spontaneous hypoglycemia. Predisposing factors to drug-induced hypoglycemia include restricted carbohydrate intake, extremes of age and abnormal liver and kidney function. In drug-induced hypoglycemia, the offending drug should be eliminated immediately and patients should receive other supportive measures to raise and maintain blood sugar levels. It is also important to avoid future recurrences. Enhanced therapeutic monitoring may be warranted when drugs with hypoglycemic potential are administered. The risk for possible drug interactions that may cause hypoglycemia increases exponentially as the number of medications in a patient's regimen increases. Although most physicians are familiar with the treatment of hypoglycemia, appropriate evaluation and follow-up of the problem require knowledge of several relatively rare diagnostic considerations.

Introduction

One of the most common endocrine emergencies in practice (1), hypoglycemia is a clinical syndrome arising from diverse causes and presents important diagnostic and therapeutic problems.

Although drug-induced hypoglycemia is more likely to occur in diabetic patients receiving hypoglycemic medications, in malnourished or debilitated patients, and in patients abusing alcohol (2-4), hypoglycemia in nondiabetic subjects, either due to various disorders they suffer or to the ingestion of drugs which have hypoglycemic potential, is also very important to recognize, diagnose and treat properly. Although a factitious cause must always be considered, it may be difficult to document.

Hypoglycemia may be associated with substantial morbidity and mortality. The diagnosis of a hypoglycemic disorder requires careful assessment of the patient for the presence of predisposing illnesses or offending drugs, and when indicated, investigation to determine the underlying cause so that proper treatment can be offered at the earliest opportunity (5).

Physiology of glucose control

Glucose is the most important fuel for normal functioning of the brain (6), although it may utilize ketone bodies in exceptional circumstances, such as prolonged starvation. Muscle tissue provides a substrate for new glucose production, but the liver is the primary source of new glucose contributed to the circulation. Other organs oxidize fatty acids in addition to glucose. Of the glucose produced from the liver, 55-60% is consumed by the brain, and the remainder by skeletal muscle, fat, formed elements of blood and renal medulla (2). The brain has an absolute dependence on glucose and is incapable of storing more than a few minutes' supply of glucose as glycogen (7). Therefore, it requires a continuous supply of glucose from the circulation.

Plasma glucose levels are maintained within a narrow range, usually between 3.3 and 8.3 mmol/l (60-150 mg/dl), despite wide variations in food intake and activity levels. This delicate balance depends on glucose influx into the circulation and glucose utilization in various tissues.

Glucose is derived from three sources: intestinal absorption following digestion of dietary carbohydrate; glycogenolysis, or the breakdown of glycogen, which is the polymerized storage form of glucose; and gluconeogenesis.

The serum glucose level during fasting or between meals is maintained primarily by the breakdown of glycogen in the liver and by gluconeogenesis. In most people, hepatic glycogen stores are sufficient to maintain plasma glucose levels for 8-12 h, but this time period can be shorter if glucose demand is increased by exercise or if glycogen stores are depleted by illness or starvation.

The postabsorptive state is the interdigestive period that begins approximately 5-6 h after a meal. However, the term is most commonly used after a 10-14-h overnight fast. In the fasting state, the rates of glucose production and utilization are equal.

The enzyme systems required to synthesize and hydrolyze glycogen are expressed in most tissues. However, only the liver and kidneys express the enzyme necessary for the release of glucose into the circulation, and also the enzymes necessary for gluconeogenesis.

As glycogen stores are depleted, glucose is generated by gluconeogenesis, which occurs primarily in the liver but also in the kidney. Gluconeogenesis requires a coordinated supply of precursors from liver, muscle and adipose tissue. Muscle provides lactate, pyruvate, alanine and other amino acids; triglycerides in adipose tissue are broken down into glycerol, which is a precursor of gluconeogenesis, and free fatty acids generate acetyl-CoA for gluconeogenesis and provide an alternative fuel source to tissues other than brain. Hepatic glucose production results from both glycogenolysis and gluconeogenesis even after an overnight fast (8). The kidneys, which both use and produce glucose, contribute little to net glucose production (9, 10). However, similar to in the liver, renal glucose production is regulated (11): it is suppressed by insulin and stimulated by epinephrine (but not by glucagon).

When fasting is prolonged to 24-48 h, gluconeogenesis becomes the sole source of glucose production (8). Amino acids are the main gluconeogenic precursors that result in net glucose formation, and as a result, muscle protein is degraded. Glucose utilization by muscle and fat virtually ceases. Because of the acceleration of lipolysis and ketogenesis, circulating ketone levels rise and it then becomes a major source of fuel for the brain. If fasting is prolonged to 40 days, ketones provide an estimated 80-90% of the energy used by the brain and renal gluconeogenesis provides up to half of the endogenous glucose production (12).

Exercise increases glucose utilization by muscle, which is severalfold greater than that in the postabsorptive state. Endogenous glucose production normally accelerates to keep a balance with the utilization so that the plasma glucose concentration is maintained.

Glucose metabolism is tightly linked to oxygen consumption in the brain. Basal glucose production is approximately 2 mg/kg/min (13), of which 55-60% is metabolized by the brain (14). When blood glucose declines, there is a parallel reduction in cerebral oxygen consumption (15).

The transfer of glucose across the blood-brain barrier, which is an insulin-dependent process, is facilitated by the glucose transport protein GLUT1 (7, 16). After traversing the capillary endothelial surface, the glucose molecule can either be processed to lactate by glial cells for presentation to the neuron, or it can be directly taken up by neuronal cells (17, 18). The GLUT3 protein helps to transport glucose directly from the interstitium (19). The glucose that crosses the blood-brain barrier is processed by astrocytes to lactate and is used by neurons as proper fuel (17, 18, 20). The epinephrine response to hypoglycemia can be decreased by infusion of large amounts of lactate (21, 22) and ketones (18, 23).

The brain can directly modulate systemic glucose concentrations (24). When the systemic glucose concentrations fall, the critical centers in the ventromedial hypothalamus can sense this. It can then trigger the release of epinephrine and glucagon when a critical glucose threshold is reached (25-28).

Hormonal balance and counterregulatory mechanisms

In humans, plasma glucose is normally maintained within a narrow range in both the fasting and fed state because of a tightly linked balance between glucose production and use (29-31). This delicate balance requires dynamic regulation of glucose influx into the circulation, as glucose utilization in various tissues can change rapidly. The glucose counterregulatory system is one of the most important homeostatic systems for the survival of mammals. It continuously protects the brain by preventing or limiting hypoglycemia under physiological circumstances such as prolonged fasting, therapeutic conditions of oral or parenteral administration of hypoglycemic drugs to patients with diabetes mellitus, as well as in factitious hypoglycemia.

The control mechanisms that maintain plasma glucose homeostasis are complex. The balance of glucose production and its uptake and utilization in peripheral tissues is exquisitely regulated by a network of hormones, neural pathways and metabolic signals. Areas of the brain, pancreatic islets, and to some extent the liver, continuously monitor plasma glucose concentrations. If hypoglycemia develops, a full spectrum of flexible responses is activated. These include the suppression of endogenous insulin secretion, the release of several counterregulatory hormones and the mobilization of nonglucose substrates. These multiple responses are all necessary for appropriate counterregulation.

Insulin, the dominant glucose-lowering hormone, suppresses endogenous glucose production and stimulates glucose utilization by insulin-sensitive tissues, thereby lowering the plasma glucose concentration. It also suppresses renal glucose production and stimulates glucose

uptake, storage and utilization by tissues such as muscle and fat. In the postabsorptive state, insulin regulates the plasma glucose concentration by inhibiting hepatic glucose production (29, 32).

Each factor's position in the hierarchy of counterregulatory forces represents the physiological importance of that factor in defending against acute hypoglycemia (31, 33-35). The first counterregulatory mechanism, namely the suppression of endogenous insulin secretion, is activated at a decrease in plasma glucose concentration of approximately 72-76 mg/dl (4.0-4.2 mmol/l) (36), whereas the release of counterregulatory hormones occurs at a plasma glucose level of approximately 67 mg/dl (3.7 mmol/l) and nondiabetic individuals may begin to experience neuroglycopenia and adrenergic symptoms characteristic of hypoglycemia (37-40).

In healthy nondiabetic subjects, the insulin concentration increases and the concentration of counterregulatory hormones decreases as the glucose concentration increases, and the opposite occurs when the blood glucose concentration decreases. In this way, insulin and the counterregulatory factors act in close relation to ensure that the blood glucose level remains stable in both the fed and fasted state. Excess amounts of insulin or insulin-like material (insulin-like growth factors IGF-1 and IGF-2), inadequate secretion of counterregulatory hormones, insufficient substrates or defects in the gluconeogenic or glycogenolytic pathways, alone or in combination, disrupt this balance and cause hypoglycemia.

Glucagon and epinephrine are critical for counterregulation of the early phase of hypoglycemia (29, 35). Their effects are also sustained during prolonged hypoglycemia. Glucagon activates glycogenolysis, and to some extent gluconeogenesis, and increases hepatic glucose production within minutes (41, 42). The kidney does not seem to be affected by glucagon stimulation (43).

In contrast to glucagon, which exerts its effects exclusively on glucose production, catecholamines exhibit multiorgan effects. They act directly to increase hepatic glycogenolysis and gluconeogenesis, effects mediated predominantly through β_2-adrenergic mechanisms (44-47), although a small, direct α-adrenergic stimulation of hepatic glucose production has been reported (48). Epinephrine stimulates lipolysis and also mobilizes gluconeogenic precursors such as lactate, alanine and glycerol (42, 49). Epinephrine limits glucose utilization by insulin-sensitive tissues predominantly through direct β-adrenergic mechanisms (44-46, 50-53). Epinephrine also suppresses endogenous secretion (54).

Within 5 years of diagnosis, diabetic patients will demonstrate a progressively impaired glucagon response in the hypoglycemic state (29), and in this setting, epinephrine secretion becomes the critical counterregulatory factor (55). Within 10 years of diagnosis, many diabetic patients will have impaired epinephrine responses, resulting in a loss of adrenergic symptoms. The combined loss of glucagon and epinephrine release results in greatly delayed recovery from hypoglycemia (56).

The effects of growth hormone and cortisol become evident a few hours after their increase in plasma. In the setting of an acute episode of hypoglycemia, increments in these hormones are not clinically relevant (35, 57-59). The hyperglycemic effect of growth hormone does not appear for several hours (60) and cortisol causes an increase in the plasma glucose level after 2-3 h (61). During protracted hypoglycemia, both hormones have a relevant role in limiting severe hypoglycemia (33, 36, 58, 62-64). Growth hormone increases glucose production and limits its use (62). Growth hormone raises plasma free fatty acid and glycerol levels, which help in stimulating gluconeogenesis and suppressing peripheral glucose oxidation and use (63). The effects of cortisol on glucose production are the result of sustained gluconeogenesis by stimulating lipolysis (54, 58).

Neural glucoregulatory factors

The sympathetic neurotransmitter norepinephrine exerts hypoglycemic actions by mechanisms assumed to be similar to those of epinephrine. Plasma norepinephrine concentrations increase during hypoglycemia, although to a lesser extent than those of epinephrine (37-39). Norepinephrine is largely an α-adrenoceptor agonist (65) but its effect during hypoglycemia is mediated through the stimulation of β-adrenoceptors (51), which is quite minimal (54). Norepinephrine, through α-adrenoceptors, may have an important role in inhibiting insulin secretion (65) and stimulating glucagon secretion (66) during hypoglycemia. It also takes part in the regulation of anterior pituitary hormones (67) and appears to be involved in the mobilization of glycogen independently of counterregulatory hormones (68).

Several investigations have suggested that the liver may have a primary glucose sensory role, but this theory remains controversial (69-74). During severe hypoglycemia, this hepatic autoregulation is activated and endogenous glucose production increases, representing an emergency system to protect the brain when other counterregulatory factors fail to prevent threatening hypoglycemia (54). Electrical stimulation of hepatic sympathetic nerves decreases glycogen content, increases glucose release and causes hyperglycemia in animals (75) and humans (76).

Neuropeptides are also released from sympathetic, parasympathetic and other neurons (77). Glycemic thresholds for various responses to declining plasma glucose concentrations in healthy subjects are quite reproducible (37-39), although these thresholds are dynamic rather than static. They shift to higher plasma glucose concentrations in subjects with poorly controlled diabetes, but recurrent episodes of hypoglycemia can lead to hypoglycemia unawareness, placing patients at increased risk for the development of severe hypoglycemia (78). Recurrent hypoglycemia has also been found to decrease the quality of life in patients with diabetes (79-81).

Drugs responsible for hypoglycemia

Drug-induced hypoglycemia is an ongoing threat, particularly for diabetic patients treated with insulin and/or oral hypoglycemic agents; it may be associated with substantial morbidity and mortality (4, 82-89).

Diabetes mellitus is a chronic, lifelong condition that can affect people of all ages, and its prevalence is increasing. It is now well established that comprehensive care makes a difference for subjects with diabetes. An important issue in diabetes treatment is proper glycemic control, because this prevents or delays the long-term complications of diabetes such as micro- or macrovascular complications (19, 90-94). However, iatrogenic hypoglycemia is the limiting factor (30, 95) in the glycemic management of both type 1 (90, 91, 96-98) and type 2 diabetes mellitus (94, 99). The inability to maintain euglycemia over time because of the barrier of hypoglycemia may explain the limited impact of aggressive glycemic therapy on the atherosclerotic complications of diabetes (90, 91, 94).

Hypoglycemia is probably the most common acute problem suffered by patients with diabetes. It is also a serious medical emergency with a potentially fatal outcome and the most common reason for patients with diabetes to present to the emergency room. It is also a major source of anxiety for diabetics, particularly those controlled on insulin, and unfortunately, in the move towards ever tighter glycemic control, it is inevitable that diabetics will continue to suffer from hypoglycemia (100).

Although severe hypoglycemia requiring assistance for recovery is an annual occurrence in almost a third of all patients with type 1 diabetes mellitus (101, 102), most episodes are treated either at home or in community settings, and less than one-third are treated by emergency medical services (103-106).

Insulin

Insulin is the mainstay of treatment for type 1 diabetic patients. However, unlike patients with type 1 diabetes who have no significant insulin secretion and hence require insulin therapy from the onset of their disease, in patients with type 2 diabetes, insulin resistance with hyperinsulinemia is a prominent feature in the early stages of the disease. Thus, type 2 diabetics benefit from measures to improve insulin sensitivity, such as caloric restriction, exercise and weight management, early in their disease. When these measures fail, glycemic goals can often be achieved with oral agents such as insulin sensitizers and insulin secretagogues. With progression of type 2 diabetes, there is ultimately a progressive loss of pancreatic β-cell function and endogenous insulin secretion. At this stage, most patients require exogenous insulin therapy to achieve optimal glucose control.

Women with type 2 diabetes also should be treated with insulin for blood glucose control, preferably started during the preconception period. During the first trimester of pregnancy, insulin requirements are similar in women with type 1 and type 2 diabetes; however, as the pregnancy proceeds into the third trimester, insulin requirements increase proportionately more in women with type 2 diabetes (107).

Insulin, together with glucose and sodium bicarbonate, is also used to treat hyperkalemia in renal insufficiency in nondiabetic patients, and diabetic patients with renal insufficiency usually receive insulin for proper diabetic control. In both the above situations there is a high risk of hypoglycemia and in almost 35% of cases episodes of hypoglycemia are reported (83).

When insulin is required, the ideal insulin replacement scheme should attempt to mimic normal human physiology. Because of imperfections in all current insulin replacement regimens, individuals with type 1 diabetes are at ongoing risk for periods of relative hyperinsulinemia with resultant hypoglycemia. Those attempting to achieve near-normal glycemic control may experience several episodes of asymptomatic or symptomatic hypoglycemia. By delivering the total daily dose with larger preprandial boluses and smaller amounts of longer acting insulin, the patient can avoid supraphysiological insulin concentrations during interprandial periods (108, 109). Although the patient may not agree initially to the need to perform more than two injections, the benefit in terms of reducing the frequency of hypoglycemia and the improved ability to predict glucose concentrations generally result in the patient accepting multiple injections (110).

Several factors affect the development of severe hypoglycemia. The duration of diabetes and insulin therapy, the degree of glycemic control, and a history of prior severe hypoglycemic reactions have been associated with a higher incidence of severe hypoglycemic reactions (111).

A relative or absolute excess in insulin mainly occurs when the dose of insulin or oral hypoglycemic drugs is excessive or when an incorrect dose is given at the wrong time. It can also occur during prolonged fasting, after exercise, in renal failure or following alcohol ingestion (111). The risk of severe hypoglycemia in insulin-requiring patients with type 2 diabetes has consistently been reported to be significantly reduced compared with the risk in type 1 diabetic patients undergoing intensive insulin therapy (90, 94, 111-114). The lower incidence of severe hypoglycemia in type 2 diabetes may result from insulin resistance, which is often quite severe (115).

Most patients with type 1 diabetes lose their ability to secrete glucagon in response to hypoglycemia shortly after developing diabetes, and thus the incremental secretion of epinephrine assumes a primary role in the hormonal response to hypoglycemia in this disease (116). Because the ability to secrete epinephrine is also impaired in approximately 25% of patients with long-standing type 1 diabetes mellitus, such patients may manifest the syndrome of “hypoglycemic unawareness”, resulting in a tendency to develop frequent, severe and prolonged hypoglycemia (117).

Sulfonylureas

Sulfonylureas were introduced into medical practice in 1955 for the treatment of diabetes and other conditions, and have been used by both diabetic and nondiabetic subjects (4, 89, 118).

The sulfonylureas resemble one another more than they differ (119), and the greatest differences are found in their blood glucose-lowering potencies and in the way in which they are eliminated from the body (85). The hypoglycemic potency of an individual agent is a function of the biological half-life of the drug itself and its active metabolites. Chlorpropamide is secreted primarily unchanged by the kidney and has the longest half-life of all sulfonylureas (35 h). It must therefore be used with extra caution in patients with impaired renal function. Tolbutamide is converted in the liver to inactive metabolites. Hepatic metabolites of acetohexamide are also hypoglycemic. Tolazamide and 3 of its 6 metabolites are hypoglycemic agents. Glipizide is converted in the liver to inactive metabolites, and glyburide undergoes hepatic transformation to 2 inactive metabolites. The largest series of sulfonylurea-induced hypoglycemic episodes –843 cases– was reported in 1985 by Campbell (120) and included 670 episodes caused by a single sulfonylurea agent, 8.4% of which resulted in death.

Sulfonylureas cross the placental barrier and stimulate hypersecretion of insulin from fetal islets (121), which leads to hypoglycemia in neonates. Life-threatening hypoglycemia developed within hours in newborn infants of diabetic mothers who had been treated during the third trimester with chlorpropamide (121-124), acetohexamide (122, 123) or tolbutamide (125).

Sulfonylureas produce hypoglycemia by releasing preformed insulin from β-cells by a direct action, and possibly by sensitizing them to the action of certain endogenous insulinotrophs such as leucine (85).

In contrast to the sulfonylureas and benzoic acid derivatives (*e.g.*, repaglinide), other oral hypoglycemic agents such as the biguanides (*e.g.,* metformin), the α-glucosidase inhibitors (*e.g.*, acarbose, miglitol) and the thiazolidinediones (*e.g.*, troglitazone, rosiglitazone, pioglitazone) do not act by stimulating insulin secretion. Therefore, with these agents, insulin levels usually decrease appropriately as plasma glucose levels fall. Nonetheless, these drugs can contribute to hypoglycemia in other ways. Thiazolidinediones, as well as metformin, can predispose to hypoglycemia in patients receiving combined treatment with insulin or an insulin secretagogue. Mechanisms invoked to explain sulfonylurea-induced hypoglycemia, especially following the administration of a second drug, include the displacement of albumin-bound sulfonylureas by more avidly binding drugs, the inhibition or competition for sulfonylurea-metabolizing enzymes in the liver (126, 127) and interference with excretion of the native drug or its metabolites (85).

Hypoglycemic reactions are less common with therapeutic doses of sulfonylureas than with insulin but are proportionately more common with glibenclamide than with other sulfonylureas (4, 89, 120, 128-132). Chlorpropamide is the next most common offender, especially in the elderly (85).

Mild sulfonylurea-induced hypoglycemia produces few symptoms and mostly they are of a subacute neuroglycopenic variety (133). Severe hypoglycemia occurs in more patients who are treated with insulin and with a duration of diabetes of over 15 years (134). Although mild hypoglycemia causes unpleasant symptoms and disrupts patients' daily activities, severe hypoglycemia can result in coma, seizures and death (134). Hypoglycemic coma has been reported in adults and children where chlorpropamide was used daily for diabetes insipidus (135-137). The intravenous tolbutamide tolerance test can induce profound coma in nondiabetic subjects (138-142). Tolbutamide was also responsible for hypoglycemia when it was used for paralysis agitans (143-145), multiple sclerosis (146) and cirrhosis (146).

Sulfonylurea-induced hypoglycemia has been documented due to accidental ingestion (147-151) and also when ingested in a suicide attempt (147, 152-155), leading to death (153, 154) or permanent brain damage (152). Sulfonylurea compounds have also been reported to cause severe hypoglycemia when prescribed simultaneously with either a second blood glucose-lowering agent or a nonhypoglycemic drug that prolongs the activity of the sulfonylurea. The different drugs which were involved include phenformin or buformin, salicylate, alcohol (156, 157), phenylbutazone (158), sulfadimidine or sulfamethoxazole for urinary tract infection (86, 159, 160), bishydroxycoumarin, azapropazone, ranitidine, cimetidine, doxepin or imipramine (89) and allopurinol (161). On some occasions, a sulfonylurea has been given by mistake by the pharmacist to nondiabetic subjects, causing severe hypoglycemia (162-166). Sulfonylureas have been used since their introduction into therapy to produce factitious hypoglycemia (130, 167-171). The causes of sulfonylurea-induced hypoglycemia in the early stages include failure to anticipate the effects of reduction in weight and adjustment in diet. Other factors include unaccustomed exercise, missed meals, and addition of one or more interactive drugs to the therapeutic regimen.

There are conflicting reports on hypoglycemia in older diabetic patients. Some studies showed that elderly patients are more vulnerable to hypoglycemia (85, 172, 173). However, Miller *et al.* (134) found that older age did not predispose patients to hypoglycemia. Several factors may contribute to the lower prevalence of hypoglycemia in older diabetic patients. First, activity levels in the elderly are likely to be lower than those in younger patients, making exercise-associated hypoglycemia less likely. Second, eating habits may be more regular in the elderly, so that missed meals causing hypoglycemia are less of a problem. Older patients may also have atypical symptoms (174) or be less symptomatic during mild hypoglycemia, and therefore not report as many episodes (134). Nevertheless, as life expectancy increases, older patients should benefit more from good glycemic control

and fear of hypoglycemia should not discourage attempts at achieving goals in the elderly (134).

Alcohol

Alcohol-induced symptomatic hypoglycemia was first described in 1942 (175) and remains an important and probably undiagnosed cause of morbidity and mortality. Ethanol overdose is the leading cause of hypoglycemic coma and death in all age groups in the United States (176). Although alcohol-induced hypoglycemia is usually found in malnourished chronic alcoholics, it also occurs in weekend spree drinkers as well, and even in occasional drinkers who have missed only a meal or two (177). It can occur in any age group, but most patients are between 20 and 40 years of age (177). A large number of cases described in the literature involve children having hypoglycemia after drinking alcohol in modest amounts or swallowing alcohol-containing mouthwash, and in infants during alcohol sponging for the alleviation of fever (177-182).

Characteristically, alcohol-induced fasting hypoglycemia develops 6-36 h after ingestion of moderate to large amounts of alcohol. The patient is usually stuporous or unconscious when first seen, but may be aggressive and uncooperative when the symptoms are attributed to alcoholic intoxication rather than hypoglycemia (183). Hypothermia is even more common than in other varieties of spontaneous hypoglycemia and may be the first clue to the correct diagnosis (133). Recurrent episodes occur but are uncommon. Alcohol can always be detected in the blood or in the breath and plasma ketone (β-hydroxybutyrate) levels are high. The incidence of hypoglycemia in alcohol-intoxicated patients presenting to emergency rooms is < 1% in adults (184-186) and 3-5% in children (182). However, alcohol is the most common cause of hypoglycemic coma (82). In one autopsy series of proven hypoglycemia, alcohol, including alcoholic liver disease, was found to be the single most common etiological agent (187).

The hypoglycemia elicited by alcohol probably occurs as a result of inhibition of hepatic gluconeogenesis (177, 188-190), although in clinical situations other factors undoubtedly have a role. Plasma insulin and C-peptide concentrations are appropriately low during episodes of alcohol-induced hypoglycemia (118, 191-195). Plasma glucagon, cortisol and growth hormone levels, although above basal values, are generally lower than would be expected based on the severity of the hypoglycemia (85). Some chronic alcoholics can tolerate extremely low blood glucose levels without neuroglycopenic symptoms (196, 197). When patients present in coma from alcohol-induced hypoglycemia, they usually recover completely following intravenous glucose. Relapse does not occur and recovery is permanent, but it may be delayed if there is any brain swelling, which is itself a bad prognostic sign (177).

Alcoholic ketoacidosis with a history of chronic excessive alcohol intake presents as an acute emergency and patients can have profound hypoglycemia. Alcohol may not have been taken for several days prior to admission and so there may be little or no alcohol in the patient's blood at the time of admission (198) and it is sometimes difficult to distinguish from diabetic ketoacidosis (197, 199). Although most patients have normal or high blood glucose levels, a significant proportion present with hypoglycemic coma (85, 200). It is wise not to give intravenous glucose to these patients before they receive thiamine by injection to prevent possible precipitation of Wernicke's encephalopathy (197, 198, 201, 202). Alcohol can potentiate insulin- (4, 89, 203-206) and sulfonylurea-induced (89) hypoglycemia.

β-Adrenoceptor antagonists

Spontaneous hypoglycemia can occur in both diabetic and nondiabetic patients receiving β-adrenoceptor-blocking drugs and was first reported by Kotler *et al.* in 1966 (207). It causes severe hypoglycemia in insulin-dependent diabetics (207-211). Infants may develop hypoglycemia when propranolol or nadolol is given for cyanotic heart disease or neonatal thyrotoxicosis (212), or when it is given to their mothers for cardiac arrhythmias, hypertension or thyrotoxicosis (213-219). Nondiabetics who are on chronic hemodialysis and propranolol therapy have developed severe hypoglycemia during hemodialysis (220-223). The use of ophthalmic timolol for the management of glaucoma was reported to cause hypoglycemia in a patient with type 1 diabetes (224), and serious hypoglycemia was reported in a man who was on propylthiouracil and propranolol for thyrotoxicosis (225).

Hypoglycemia due to nonselective β-adrenoceptor antagonists may have a fatal outcome (226, 227). Most cases have involved either diabetic patients receiving insulin or sulfonylureas, or children who are particularly susceptible to the hypoglycemic action of these agents, even when taken at normal therapeutic doses (228-230).

The mechanism of action of β-adrenoceptor-mediated hypoglycemia involves inhibition of hepatic glucose production, which is promoted by sympathetic nervous system stimulation (231). By reducing lipolysis and thereby lowering plasma nonesterified fatty acid concentrations, β-adrenoceptor antagonists may increase peripheral glucose uptake by muscle and indirectly reduce gluconeogenesis (232). β-Adrenoceptor antagonists, particularly noncardioselective agents, may intensify hypoglycemia once present and delay recovery (233). They also blunt the counterregulatory effects of epinephrine, with a resultant reduction in glycogenolysis, which may not only cause hypoglycemia but also prolong the duration of the episode (234). Failure of a plasma glucagon increase in response to insulin-induced hypoglycemia was also observed in normal subjects taking therapeutic doses of the nonselective β-adrenoceptor blocker propranolol (235).

The effects of β-adrenoceptor blockade on the symptomatology of acute neuroglycopenia are controversial. Some studies have noted no effect on the incidence and severity of symptoms of hypoglycemia, whereas others have found attenuation of the signs and symptoms of hypoglycemia (85, 133, 176). Perspiration is usually enhanced and may serve as a hallmark of hypoglycemia in these patients (234). Cardioselective agents tend to cause less alteration in hypoglycemic symptoms than do noncardioselective agents (176, 231).

Angiotensin-converting enzyme inhibitors

Hypertension, congestive cardiac failure and myocardial infarction are common among patients with diabetes mellitus. Most of these disorders necessitate long-term drug treatment. Many antihypertensive drugs, such as thiazide diuretics and β-blockers, have adverse effects on glucose metabolism. Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive agents with few side effects compared with other drugs (236). They are considered a first-line choice in the treatment of hypertension in patients with diabetes (237, 238) because they do not increase lipid or blood glucose levels or decrease urinary albumin excretion rate (239-241), and may prevent the progressive deterioration in renal function seen in diabetic nephropathy (239, 240).

The association between the use of ACE inhibitors and episodes of hypoglycemia in patients with diabetes is controversial. There are reports that ACE inhibitors were responsible for a reduction in insulin requirements or even discontinuation of oral hypoglycemic agents (242, 243). In some cases, hypoglycemic episodes were attributed to the use of an ACE inhibitor (244-246), although other authors urged caution when interpreting these results (247-249) because of the presence of comorbid conditions such as heart failure or renal failure.

The mechanisms of hypoglycemia during ACE inhibitor therapy have not been clarified. Some investigators found increased insulin sensitivity, probably due to enhanced insulin-mediated peripheral glucose disposal from muscular tissue (242, 250-253), but others failed to show any effect of ACE inhibitors on glucose metabolism (254-258). The notion that ACE inhibitors might improve insulin sensitivity is based in part on the assumption that angiotensin II has diabetogenic effects in peripheral tissues, similar to other counterregulatory hormones such as catecholamines (259). Other investigators have shown that angiotensin II increases insulin sensitivity in both diabetic and nondiabetic subjects (260, 261). Some authors (262) documented that captopril accelerates the absorption of subcutaneous insulin and this could be an additional mechanism causing hypoglycemia in insulin-dependent diabetic patients. Angiotensin-converting enzyme inhibitors have been shown to increase bradykinin levels, and Jauch *et al*. (263) have shown that bradykinin infusions can decrease hepatic glucose production. Thus, when ACE inhibitors are given together with some form of hypoglycemic treatment, different hypoglycemic mechanisms may act together and potentiate the effects of each drug. Tight glycemic control and the increasing use of ACE inhibitors could result in an increase in admissions for hypoglycemia caused by the drugs.

Quinine and quinidine

The antimalarial drug quinine and its stereoisomer quinidine are known to induce hypoglycemia in some individuals (264-268). The first case report of quinine-induced hypoglycemia appeared in 1925 (269). When used for severe falciparum malaria, quinine can cause profound hypoglycemia (264, 270), leading on occasion to death (265). An asymptomatic case has been reported following treatment for muscle cramps with quinine (271). Jones *et al*. (265) reported a case of severe symptomatic hypoglycemia in a patient with terminal renal failure who had been treated for muscle cramps with quinine.

Quinine-induced hypoglycemia is a dose-dependent phenomenon and quinine sulfate in high doses may cause insulin-mediated hypoglycemia in healthy persons (272). Although confounding conditions may contribute to hypoglycemia, these compounds are capable of stimulating insulin release from the pancreas (264, 266, 267). Insulin release from isolated pancreatic islets of Langerhans is stimulated by quinine *in vitro* (273). It increases the insulinotropic effect of glucose and also stimulates the release of insulin at low glucose concentrations, probably through the activation of voltage-sensitive calcium channels by inhibition of potassium conductance (274). Quinine is normally excreted via the kidneys and the high plasma concentrations reflect drug accumulation due to renal failure, which might be responsible for inappropriate β-cell secretion of insulin (265).

Pentamidine

Pentamidine is a biguanide derivative that was first reported to induce hypoglycemia in a patient with non-Hodgkin's lymphoma given the drug to treat *Pneumocystis carinii* infection (275). Since then, many case reports of pentamidine-induced hypoglycemia have appeared (276-282).

Hypoglycemia occurs in approximately 6-40% of patients treated with pentamidine and is considered to be the most common metabolic abnormality associated with this drug (176). With the onset of the AIDS epidemic, the use of pentamidine for the treatment of *P. carinii* pneumonia (PCP) has increased markedly, and dysglycemia due to the use of this drug has become a serious problem (283-285). The prevalence of hypoglycemia is higher in patients with AIDS than in other patients (286). Hypoglycemia and diabetes have also been reported after pentamidine aerosol therapy (287-292). The reaction is usually observed within days after therapy is initiated,

although it can occur within a few hours (281). The hypoglycemia is often recurrent and severe, and sometimes results in irreversible neurological damage (281). It is caused by a cytolytic response in the pancreas accompanied by a release of preformed insulin with the subsequent development of hypoglycemia; as pancreatic destruction progresses, patients may eventually become insulin-deficient and diabetic (276, 281, 286, 293-296).

Disopyramide

Disopyramide has quinidine-like activity and is used as an antiarrhythmic drug (297). It is now one of the most common causes of nonantidiabetic drug-induced hypoglycemia (298-305). Disopyramide stimulates insulin secretion and can lead to hyperinsulinemic hypoglycemia (85, 299). Old age and impaired renal function present a serious risk factor (298), as its half-life is prolonged in renal failure (300).

Salicylates

Salicylates were used in the past as hypoglycemic agents but their use was short-lived because of the toxicity associated with the high doses needed to consistently lower blood glucose (306). Symptomatic hypoglycemia due to salicylates has been reported on a number of occasions, especially in young children (307-313), sometimes leading to death (4). It is not generally known that therapeutic amounts of salicylates are as potent as some sulfonylurea compounds and biguanides in lowering blood glucose in diabetics and nondiabetics alike (314-316). They can cause hypoglycemia in adults when used alone (141) or in combination with other antidiabetic agents (317, 318).

Although the precise mode of the hypoglycemic action of salicylates remains uncertain (306), possible mechanisms include decreased hepatic gluconeogenesis and increased insulin secretion (319), possibly due to the ability of salicylates to act as cyclooxygenase inhibitors and suppressors of endogenous prostaglandin E production by pancreatic β-cells (320), increased peripheral glucose utilization owing to uncoupling of oxidative phosphorylation, or reduced circulating nonesterified fatty acid levels due to suppression of lipolysis (321). Salicylates may also increase insulin sensitivity, displace sulfonylureas from protein binding sites and inhibit renal excretion (176, 321).

Trimethoprim/sulfamethoxazole

Sulfa-based antibiotics may potentiate the hypoglycemic effects of sulfonylureas (160) and also may produce hypoglycemia without concomitant sulfonylurea administration (322). There are case reports where trimethoprim/sulfamethoxazole was thought to be responsible for hypoglycemia (323-326). Malouf and Brust reported a fatality attributable to hypoglycemia following administration of trimethoprim/sulfamethoxazole along with chlorpropamide (82). Because of their structural similarities to sulfonylureas, sulfonamides are liable to facilitate hypoglycemia by increasing insulin release in susceptible individuals (323, 325, 326).

Tryptophan and monoamine oxidase inhibitors

Although they are used quite extensively in clinical practice, there are very few reports of hypoglycemia induced by these agents (327). Tryptophan, 5-hydroxytryptophan and certain monoamine oxidase (MAO) inhibitors can induce hypoglycemia when given in large doses (328, 329). It seems that the hydrazine group present in MAO inhibitors is responsible for the hypoglycemic action (330). Inhibitors of MAO have been reported to potentiate the hypoglycemic action of endogenous insulin (331).

Sertraline

Unlike other selective serotonin reuptake inhibitors (SSRIs), sertraline has linear pharmacokinetics so that increases in dose lead to proportional increases in drug concentration. The half-life of sertraline is about 26 h and it reaches steady state in 1 week. Hypoglycemia associated with sertraline and coadministration of oral hypoglycemics belonging to the sulfonylurea class has been reported (332, 333). Although the exact mechanism has not been elucidated, it may be through inhibition of cytochrome P-450 enzymes.

Ciprofloxacin

Ciprofloxacin, a widely used quinolone antibiotic, is a recognized P-450 enzyme inhibitor. Conflicting data exist in the medical literature on the ability of quinolone antibiotics to inhibit the hepatic metabolism of oral hypoglycemic agents such as glyburide. Roberge *et al.* (127) documented a case of hypoglycemia and elevated serum glyburide levels after 1 week of ciprofloxacin use in a patient receiving long-term glyburide therapy. Clinicians should consider this potential interaction in patients taking drugs such as glyburide who require this type of antibiotic.

Bordetella pertussis vaccine

Infection or vaccination of infants with *Bordetella pertussis* has been reported to be associated with hypoglycemia (334, 335). *In vivo* studies in animals suggest that *B. pertussis* can cause hyperinsulinemia with a resultant hypoglycemic response (336-338). However, infants

with clinical pertussis or following vaccination have developed hyperinsulinemia without any hypoglycemia (338-340). *Bordetella pertussis* acts to amplify the insulinogenic response to primary stimuli such as glucose (338), and it is thought that the islet-activating protein of *B. pertussis* augments the generation of cAMP in islet β-cells (341) through inactivation of the G_i subunit of adenylate cyclase (342).

Paracetamol

Paracetamol at normal analgesic doses was implicated as a cause of hypoglycemia in a child who also had salicylate-induced hypoglycemia (312). Paracetamol poisoning can be responsible for acute hepatic necrosis leading to symptomatic hypoglycemia (343, 344).

Lithium

It has been reported that lithium may potentiate the hypoglycemic effect of antidiabetic drugs (345, 346).

Hemodialysis

Patients undergoing hemodialysis may become hypoglycemic and not be aware of it. Hypoglycemia in this case is not caused by a hormonal imbalance, but the hormonal response to hypoglycemia is blunted. Patients with an initial plasma glucose concentration of 5.5 mmol/l (100 mg/dl) or less who are given hemodialysis and who do not eat during dialysis may be particularly at risk, especially if they are on insulin or glucose-lowering medications. They should be dialyzed with a dialysis fluid containing at least 5.5 mmol/l (100 mg/dl) glucose (347).

Vacor

Vacor is a rodenticide containing *N*-3-pyridylmethylurea (PNU), which is chemically related to alloxan and streptozotocin (348). Vacor is a potent β-cell toxin that initially produces severe hypoglycemia by washing out stored insulin, followed by complete destruction of β-cells and fatal diabetes (349). Accidental ingestion of Vacor has resulted in severe hypoglycemia (349). It is suggested that the mechanism of Vacor toxicity involves niacinamide antagonism (350).

Ritodrine

Hypoglycemia has been documented often in infants born to mothers who have received ritodrine treatment during pregnancy to delay premature delivery (351), but only rarely occurs in the mother (352). Ritodrine-induced hypoglycemia has been attributed to its insulin-secretory action because of high plasma insulin and C-peptide levels.

Salbutamol

Symptomatic hypoglycemia caused by salbutamol overdose has been recorded in a single case report in a 16-month-old infant, possibly as a result of stimulation of insulin secretion (353).

Akee fruit

Akee fruit is mainly eaten in Jamaica, where it is a dietary staple. Several hours to a few days after eating this unripe fruit, the patient develops retching, vomiting, convulsions, coma and death. It is associated with profound hypoglycemia and is believed to produce hypoglycin A, which inhibits hepatic gluconeogenesis (354, 355).

Miscellaneous drugs

Single case reports of alleged drug-induced hypoglycemia are usually clinically insignificant. A causal relationship has not been established for many of these agents. These episodes have almost always occurred in undernourished elderly patients with or without concomitant liver or kidney disease. The following drugs have been reported in the literature to be the cause of isolated cases of drug-induced hypoglycemia: amphetamine (356), benzodiazepines (128), cibenzoline (357), dicumarol (358, 359), ecstasy (MDMA) (360), enflurane (361), ethionamide (362), ethylenediamine tetraacetate (363), etomidate (364), fluoxetine (365), formestane (366), furosemide (128), gatifloxacin (367), haloperidol (368), halofenate (369), halothane (370), herbal extracts (371), indomethacin (372), interferon (373), isoniazid (362, 374), lidocaine (375), manganese (376), maprotiline (377), mefloquine (378), nefazodone (379), octreotide (380), orphenadrine (381), oxytetracycline (382), *para*-aminobenzoic acid (383), *para*-aminosalicylic acid (384), phenothiazine (381), phenylbutazone (358), phenytoin (385), piroxicam (372), propoxyphene (386, 387) and selegiline (388).

Clinical manifestations

Although they are often typical, symptoms of hypoglycemia are nonspecific. Symptomatic hypoglycemia is common and associated with almost limitless combinations of signs and symptoms (389).

Children and the elderly are especially susceptible to hypoglycemia (89, 128, 390-393). The very young have disproportionately high brain requirements for glucose (394) and the elderly may have associated health

problems, such as hepatic or renal impairment, that increase the hypoglycemic action of drugs, and they may also have reduced cognitive function, which magnifies the effects of even minor degrees of hypoglycemia.

Symptoms can be attributed to hypoglycemia only when Whipple's triad (395) is fulfilled, that is, the symptoms are consistent with hypoglycemia, low plasma glucose concentrations are present and the symptoms are relieved after plasma glucose is raised.

The symptoms of hypoglycemia in adults may be quite varied, but in any one individual the symptom complex tends to be quite consistent (396, 397). The symptoms can be divided into two categories: neurogenic (or autonomic) and neuroglycopenic symptoms (30, 398). Even though the symptoms have been divided into these two categories, they all reflect the effects of hypoglycemia on the central nervous system. The neurogenic symptoms may mimic several other entities, including anxiety attacks and hyperventilation (399), The neuroglycopenic symptoms have been misdiagnosed as being due to epilepsy, personality disorder, chronic nervous exhaustion, psychosis, hysteria, menopause or inebriation (400). Although the symptoms of hypoglycemia in children may be similar to those in adults, this is not true for the newborn and infants, who manifest irritability, feeding difficulties, lethargy, cyanosis and tachypnea when the plasma glucose level is low (5).

Neurogenic symptoms

Hypoglycemia activates glucose-sensitive neurons, including those in the ventromedial hypothalamus, which are responsible for adrenergic nervous system discharge (401). These symptoms may be mediated by a circulating hormone such as epinephrine, or by a neurotransmitter. Adrenergic symptoms include palpitations, anxiety and tremulousness (53, 402, 403). Cholinergic (acetylcholine-mediated) symptoms include sweating, hunger and paresthesia (402, 404). Hunger may arise from a peripheral signal (405). Angina in the presence of normal coronary arteries has been reported during hypoglycemia (406). Other documented adrenergic symptoms are nervousness, irritability, pallor, nausea and flushing (5).

Neuroglycopenic symptoms

The brain is vitally dependent on glucose for its normal functioning and is unable to store or synthesize glucose. Hypoglycemia causes cortical lesions, especially in the temporal lobes, is associated with elevated tissue pH, and injures middle layers of the cerebral cortex and hippocampus, while sparing the brain stem and spinal cord (407). The inability of the brain to utilize oxygen at low blood glucose levels despite normal cerebral blood flow and arterial oxygen tension results in impaired brain function (408, 409). Although there is individual variation, the threshold for neuroglycopenic symptoms is approximately 36 mg/dl (410). Below this level, changes in the electroencephalogram and behavior are observed, but it has been difficult to demonstrate any deficit in cerebral energy (411).

Neuroglycopenic symptoms include difficulty in thinking or confusion, a sensation of warmth or cold, weakness and fatigue, headache, blurred vision, paresthesia, dizziness, amnesia, incoordination, difficulty waking in the morning and organic personality syndrome (5, 398). In more severe cases, patients can manifest cognitive failure, behavioral changes, seizures, coma and ultimately death (412-414).

There is no consistent chronological order to the evolution of symptoms. Autonomic symptoms do not always precede neuroglycopenic symptoms, and many patients experience only neuroglycopenic symptoms (397, 415).

Physical signs

Transient hemiparesis, aphasia, positive Babinski reflexes or localizing neurological abnormalities may present during hypoglycemia (392, 416-420). The neurological findings usually clear completely after administration of glucose and restoration of plasma glucose to normal.

Mechanisms involved in producing these neurological abnormalities include underlying brain disease, selective neuronal vulnerability, or structural defects or spasm of cerebral blood vessels (418). Convulsions appear to be more common in children with hypoglycemia (421). Both decerebrate rigidity and decorticate posturing have been observed during hypoglycemia and were reversed by glucose administration (417). Senile dementia (422) and organic personality syndrome (423) may result from unrecognized hypoglycemia. The pathogenesis of visual changes in hypoglycemia is more complex (424). Although visual acuity remains normal, color vision is significantly impaired and correlates well with the fall in plasma glucose. Visual evoked potentials are significantly prolonged during hypoglycemia and the reaction time to visual stimuli is decreased (425).

Other common signs of hypoglycemia include pallor and diaphoresis. Heart rate increases and the pulse pressure widens, which is mediated by the adrenergic nervous system (53). Premature atrial and ventricular contractions have been described during hypoglycemia (426). Repeated episodes of hypoglycemia can give rise to a predominantly motor-sensorimotor peripheral neuropathy (427-430). Fasciculations have occasionally been reported and tendon reflexes may be exaggerated (426) or depressed (427). Both hypothermia (431, 432) and hyperthermia (433, 434) have been associated with hypoglycemia. A β-adrenergic mechanism is responsible for heat production (435) and hypothermia results from accelerated heat loss caused by peripheral vasodilatation, increased sweating and inhibition of shivering (436).

The magnitude of the responses to hypoglycemia is an inverse function of the nadir plasma glucose concentration rather than the rate of decrease in plasma glucose

(59, 437, 438). The relative paucity of symptoms at a given low plasma glucose concentration in individuals with recurrent hypoglycemia, such as those with tightly controlled diabetes (439) or with an insulinoma (440), is attributable to a shift in glycemic thresholds for responses to lower plasma glucose concentrations. Conversely, the threshold shifts to higher plasma glucose concentrations in patients with chronic hypoglycemia, resulting in symptoms of hypoglycemia at relatively high glucose levels (441). The generation of symptoms of hypoglycemia or their perception may be blunted by ethanol, sedatives, β-adrenoceptor-blocking agents, supine position (396) and defective counterregulation (440, 442, 443).

Diagnosis

In patients with documented hypoglycemia, a plausible hypoglycemic mechanism and further diagnostic evaluation can be guided by history, physical examination and available laboratory data. An accurate history is of immense importance, as it will determine the sequence of investigations designed to confirm or refute the diagnosis, but it may be difficult to obtain. Sometimes the history is not reliable, as hypoglycemia itself distorts memory of events. Independent corroboration of the patient's story is therefore essential (444). In accidental and factitious hypoglycemia, the proper history is usually difficult to elucidate and suspicion of factitious disease is the first step toward correct diagnosis. The problem is most frequent in women, in health professionals and relatives of insulin-taking diabetic patients (445, 446).

Although the patient's history is of fundamental importance in determining the possibility of hypoglycemia, the diagnosis cannot be made solely on the basis of signs and symptoms. Therefore, most of the time the patient requires further testing to determine the diagnosis for appropriate management.

A normal plasma glucose level reliably obtained during the occurrence of spontaneous symptoms eliminates the possibility of a hypoglycemic disorder (447). Often however, the measurement of plasma glucose is not feasible when spontaneous symptoms occur during activities of daily life. The diagnosis of hypoglycemia should thus not be made solely on the basis of plasma glucose measurement unless it is unequivocally below normal. It is very difficult to define a cut-off value for hypoglycemic symptoms. Although symptoms commonly occur with plasma glucose levels below 3.0 mmol/l (54 mg/dl) (37-39), they can occur at higher plasma glucose levels in poorly controlled diabetes (439, 441), or in other conditions such as insulinoma (440) which can give rise to recurrent hypoglycemia. Confirmation that a patient's symptoms are caused by hypoglycemia has been facilitated enormously by the ability to teach patients, or their relatives, how to collect blood for glucose analysis during spontaneous episodes occurring in the course of everyday life.

It is useful to initially place hypoglycemia in the category of hyperinsulinemic or hypoinsulinemic. This is achieved by measuring insulin, C-peptide and proinsulin concentrations in peripheral venous blood plasma (448, 449). Elevation of both plasma total immunoreactive insulin (IRI) and C-peptide is strong evidence of endogenous hyperinsulinemia, including the surreptitious use of sulfonylureas. However, elevated IRI in the presence of reduced C-peptide suggests exogenous hyperinsulinemia (450). A suppressed plasma proinsulin concentration in a patient with proven endogenous hyperinsulinism may indicate sulfonylurea-induced factitious hypoglycemia (448).

In addition to the amount of insulin, determination of the species of insulin may be useful in distinguishing between an insulin-secreting tumor and surreptitious use of insulin, unless it is human insulin that is being injected (5). Insulin from different species can be distinguished by high-pressure liquid chromatography (451) or by the use of species-specific insulin antibodies (452-454), although it is very rare nowadays with the widespread use of biosynthetic human insulin.

Determination of a lack of suppression of plasma C-peptide during insulin-induced hypoglycemia is indicative of islet cell tumor (455, 456) or surreptitious use of sulfonylureas (457) as the cause of hypoglycemia.

A definitive diagnosis of factitious hypoglycemia is difficult (458). Some biochemical indices such as hyperinsulinemia can mimic an insulin-secreting tumor (459). Assays for proinsulin-like activity and C-peptide (448, 460, 461), tests inducing modulation of insulin secretion and radiolabeling of the patient's insulin (457) have proven useful in some cases.

Measurement of plasma levels of drugs is helpful in hypoglycemia caused by abuse of oral hypoglycemic agents (462, 463). First-generation sulfonylureas are readily detectable by this method. Second-generation sulfonylureas do not volatalize as readily as the first-generation compounds and therefore are not readily detectable by a gas chromatography-mass spectrography method (447). Confirmation of a suspected diagnosis of sulfonylurea-induced hypoglycemia can be made by demonstrating the presence of sulfonylurea in the blood by high-pressure liquid chromatography or radioimmunoassay (171, 447, 464-466). This latter technique is particularly useful for screening, but cannot distinguish between the different types of sulfonylureas.

Treatment

In view of the vulnerability of the brain to prolonged hypoglycemia, plasma glucose concentrations must be elevated at least to normal levels as rapidly as possible and the recurrence of hypoglycemia must be prevented.

Although severe hypoglycemia requiring assistance for recovery is an annual occurrence in almost a third of all patients with type 1 diabetes (101, 102), most episodes are treated either at home or in community settings

since the symptoms of hypoglycemia are well known to the patients and/or their relatives; less than one-third are treated by emergency medical services (103-106). Although some diabetic patients are treated in the emergency room, most patients do not require admission to hospital because recovery is usually rapid.

High morbidity and mortality are still associated with hypoglycemia, and although the precipitating cause is not always found (88, 103, 467), an accurate diagnosis and early treatment may improve the prognosis. Since outcome depends on how soon the condition is recognized and treated, the only foolproof rationale is to assume that every unconscious patient is in hypoglycemic coma until proven otherwise.

Management falls quite clearly into two separate phases: first, symptomatic treatment of the acute episode, and second, investigation of the cause so that specific treatment of the primary disease or offending agents causing hypoglycemia can be offered at the earliest opportunity. If the patient is hypoglycemic when seen, urgent treatment is often necessary. When possible, a sample for measurement of plasma glucose concentrations by a quantitative analytical method should be obtained prior to treatment. The potential detrimental effects of delayed treatment of hypoglycemia far outweigh any ill effect of unnecessary treatment. In addition, if the hypoglycemic mechanism is not clear, plasma samples for insulin, C-peptide, sulfonylureas and ethanol, at least, should be obtained before glucose administration, as the opportunity for a reliable diagnosis may otherwise be irretrievably lost.

Most episodes of asymptomatic hypoglycemia and mild to moderate symptomatic hypoglycemia are treated effectively by the ingestion of glucose or carbohydrate, although the choice will depend on what is available to the patient at the time of hypoglycemia (468-470). A commonly recommended dose of glucose is 20 g (0.3 g/kg in children) (108). Eating more does not accelerate the rate of recovery to normal and may cause hyperglycemia in the hours following the reaction (110). However, the glycemic response to oral glucose is transient, usually less than 2 h in insulin-induced hypoglycemia in type 1 diabetes mellitus (468). Thus, ingestion of a more substantial mixed snack or meal shortly after the plasma glucose level is raised is generally advisable. The advantage of drinking milk lies in the more prolonged rate of starch absorption owing to the protein and fat in addition to the carbohydrate (471).

Parenteral treatment is necessary when the patient is unable or unwilling to take carbohydrate orally. In an emergency situation, the patient may be incapacitated to the point of being unable to recognize the seriousness of the situation. Some patients are obstreperous, belligerent and combative when assistance is urged on them. Intravenous glucose, 25 g initially, is the standard therapy but the quantities of glucose required can only be assessed by constant monitoring of blood glucose levels and are often very large. Intravenous glucose should be continued until all of the insulin, sulfonylurea or the offending drug has been absorbed and degraded metabolically (472). As many as 80 g/h of glucose may be required for up to 60 h, depending on the dose and type of insulin or sulfonylurea used and the site of injection (118, 473-478). This quantity of glucose can only be given safely as a 25-50% solution through a central line followed by a constant infusion of 5% or 10% dextrose (472).

If intravenous therapy is not practical, subcutaneous or intramuscular glucagon can be given by a spouse or family member (468, 469, 479-481), particularly in subjects with type 1 diabetes mellitus. The standard dose, 1 mg (15 μg/kg in children), can cause substantial but transient hyperglycemia (468). It takes 10-20 min to be absorbed from the site and for glycogen to be mobilized subsequently from the liver. The duration of action of this treatment is 60-120 min (110). Intranasal administration of glucagon causes a glycemic response similar to injected glucagon (482-484). Glucagon may not work if there is hepatic glycogen depletion, as may happen when the primary cause is alcohol or paracetamol poisoning (444), or the patient is malnourished. It is also been suggested that glucagon probably should be avoided in type 2 diabetic patients because it can stimulate endogenous insulin secretion (485).

Diazoxide, an antihypertensive agent that prevents insulin release, may be considered in conjunction with glucose infusion (130, 486, 487), but it is not very effective and only partially successful (110).

Octreotide, a somatostatin derivative, is another therapeutic option. It is a potent inhibitor of insulin and glucagon release from the β-cells of the pancreas (488). Octreotide is quite safe and effective in preventing rebound hypoglycemia after sulfonylurea ingestion. Octreotide in combination with dextrose is even considered as first-line therapy in the treatment of sulfonylurea-induced hypoglycemia (489). Octreotide is usually used as an infusion, although it can be given subcutaneously. There are reports where octreotide was used to treat hypoglycemia and could obviate the need for dextrose infusion (490-492).

There is evidence that the decreased availability of glucose precursors, promoted by insulin administration, limits the participation of hepatic gluconeogenesis in glycemia recovery. However, the administration of gluconeogenic precursors could overcome this limitation and promote better glycemic recovery than glucose itself (493).

Hypoglycemia caused by drugs is limited to the duration of action of the offending drug. The drug should be discontinued either completely, or temporarily if the drug is essential, and then the dose can be adjusted to avoid recurrent hypoglycemia. Safe plasma glucose levels should be maintained while the offending drug action continues.

Sequelae

A correlation between the frequency of severe hypoglycemia and the magnitude of intellectual decline has

been observed in patients with diabetes mellitus who were treated with insulin (494). However, in the Diabetes Control and Complications Trial in which patients were enrolled for an average of 6.5 years, despite a 3-fold increase in severe hypoglycemia in patients on intensive insulin therapy compared with those receiving conventional therapy, there was no difference in neuropsychological function (90). Children may be at risk for cognitive impairment from recurrent severe hypoglycemia (495). Convulsions arising from hypoglycemia have been seen to result in serious musculoskeletal injuries (496, 497).

Most reports of hypoglycemia-related morbidity emphasize the effects of neuroglycopenia on the central nervous system, or associated vascular events such as myocardial infarction, stroke and cardiac arrhythmias (497). Hypoglycemia is still associated with mortality (82, 83, 413, 498-501), but there appears to have been no increase in deaths from hypoglycemia in the U.K. following the introduction of human insulin for routine care (502). Although it is clear that hypoglycemia can produce death, the exact mechanism is not known. The only anatomic abnormality found to account for death has been myocardial infarction of greater or lesser severity (503, 504). Autopsy performed within approximately 24 h after death from hypoglycemia did not reveal any classic histopathological changes (187). Sometimes when death follows a hypoglycemic coma lasting for 12 h or more, neuroanatomic changes can occur (505, 506), and there are reports of deaths following insulin tolerance tests which were probably a consequence of cardiac dysrhythmia (503, 507).

Prevention

Prevention of recurrent hypoglycemia requires a proper understanding of the underlying mechanism. It should be remembered that hypoglycemia caused by sulfonylureas may recur after a period of many hours or days.

In addition to regimen adjustments for patients who are on insulin, approaches to the problem of nocturnal hypoglycemia include the use of newer insulin analogues and bedtime treatments. Substitution of a preprandial rapid-acting insulin analogue (*e.g.*, insulin lispro or aspart) for short-acting (regular) insulin during the day reduces the frequency of nocturnal hypoglycemia (508). Again, using a long-acting insulin analogue (*e.g.*, insulin glargine) in place of NPH or ultralente insulin at bedtime may reduce the frequency of nocturnal hypoglycemia (509). Bedtime treatments including snacks (510), uncooked cornstarch (511, 512), the glucagon-releasing amino acid alanine (471, 510) or the epinephrine-stimulating β_2-adrenoceptor agonist terbutaline (471, 510) have been used to reduce nocturnal hypoglycemia.

In iatrogenic hypoglycemia, the principles of aggressive glycemic therapy should be adjusted accordingly to include frequent self-monitoring of blood glucose by the patient, flexible drug (oral hypoglycemics and insulin) regimens, proper education of the patient and relatives, and ongoing professional guidance and support.

When the duration of effects of large doses of insulin, sulfonylureas or other drugs is not taken properly into account, patients can be discharged prematurely from the hospital following relief of acute factitious hypoglycemia. In this situation, there is a possibility of recurrence of hypoglycemia, which, if severe, can lead to coma, permanent brain damage or death (513). Therefore, these patients require prolonged observation even though this may impose enormous logistical problems (83, 207, 514).

In factitious hypoglycemia, intensive psychiatric therapy is recommended after the diagnosis is established to prevent long-term morbidity and mortality, as they are associated with a poor long-term prognosis (449, 515). Unfortunately, this is often unsuccessful (448, 449, 515-518).

Conclusions

Therapeutically administered antidiabetic drugs such as insulin and the sulfonylureas are undoubtedly the most common cause of hypoglycemia encountered in clinical practice, and the benefits and risks of treatment must therefore be weighed. Hypoglycemia can be an important limiting factor in the treatment of patients with diabetes mellitus, but there are also many other drugs which can produce hypoglycemia in seemingly healthy individuals.

The diagnosis of a hypoglycemic disorder requires careful assessment of the patient for the presence of offending drugs or predisposing illnesses, and appropriate further testing if necessary, to reach a correct diagnosis. Unless the true cause is identified when the patient is first seen, fruitless and expensive testing may ensue.

Although severe hypoglycemia is a rare cause of acute emergency admission to hospital, it is associated with significant morbidity and mortality, requires careful treatment and follow-up, and may identify high-risk patients with a poor prognosis. Drug-induced hypoglycemia continues to be so common that virtually every unconscious patient should be considered hypoglycemic until proven otherwise.

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