Drug-Induced Hypoglycemic Coma in 102 Diabetic Patients

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Background: Hypoglycemic coma is a continuous threat for diabetic patients treated with insulin and/or oral hypoglycemic agents; it may be associated with substantial morbidity and mortality.

Methods: We retrospectively reviewed our clinical experience with drug-induced hypoglycemic coma during a 7-year period.

Results: The study consisted of 102 patients and included 61 females and 41 males. The median age was 72 years. Ninety-two patients suffered from type 2 diabetes mellitus; 10 patients had type 1 diabetes mellitus. The median lowest blood glucose level was 1.77 mmol/L (32 mg/dL). Drug-induced hypoglycemic coma occurred in 99 patients out of the hospital, while 3 patients developed it during hospitalization. Drug-induced hypoglycemic coma occurred in patients undergoing treatment with insulin, glyburide, and combined therapy with insulin and glyburide, insulin and metformin, or glyburide and metformin. Ninety-three patients had at least 1 of the following risk factors: age older than 60 years, renal dysfunction, decreased intake of energy, and infection. Fourteen patients concomitantly received drugs that potentiated hypoglycemia. Forty patients responded to treatment within the first 12 hours, while 62 patients had protracted hypoglycemia of 12 to 72 hours' duration. Morbidity included physical injuries in 7 patients, myocardial ischemia in 2 patients, and stroke in 1 patient. Death occurred in 5 patients.

Conclusions: Hypoglycemic coma is a serious and not an uncommon problem among elderly patients with diabetes mellitus and treated with insulin and/or oral hypoglycemic drugs. Risk factors contribute substantially to the morbidity and mortality of patients with drug-induced hypoglycemic coma. Enhanced therapeutic monitoring may be warranted when hypoglycemic drugs are administered to an elderly patient with the above predisposing factors and potentiating drugs for hypoglycemia.

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Diabetic patients who are treated with insulin and/or hypoglycemic drugs are at a greater risk of suffering hypoglycemic episodes than diabetic patients treated by diet only, a fact that has been supported by the widespread systemic monitoring of blood glucose during the last decade.1,2 The inability of the brain to utilize oxygen at low blood glucose levels despite normal arterial oxygen tension results in impaired brain function.3 Drug-induced hypoglycemia is an ongoing threat for diabetic patients treated with insulin and/or oral hypoglycemic agents; it may be associated with substantial morbidity and mortality.5-26 Although publications document the occurrence of drug-induced hypoglycemic coma (DIHC), no recent study directly addresses this issue. The purpose of this study is to describe our clinical experience with DIHC in 102 patients.

Of 102 patients, 61 (59.8%) were female and 41 (40.2%) were male. The median age was 72 years; the age distribution of the patients is depicted in Figure 1. Ninety-two patients had type 2 diabetes mellitus and 10 patients had type 1 diabetes mellitus; knowledge by the patient of his or her condition ranged from 1 to 41 years (median, 10 years).

Drug-induced hypoglycemic coma was the primary cause for hospital admission in 99 patients and occurred during hospitalization in 3 patients. The DIHC occurred in patients treated with a variety of commonly prescribed diabetic medications (Figure 2). Figure 3 illustrates the distribution of blood glucose levels on admission (median, 1.77 mmol/L [32 mg/dL]). Reduced energy intake was caused by a lack of appetite, inability to eat, or nutrient loss (vomiting, diarrhea).

Ninety-three patients had risk factors for DIHC (Figure 4); of these, 27 patients (26.4%) had both renal dysfunction and reduced energy intake. Fourteen patients were concomitantly medicated with hypoglycemia-potentiating drugs, including β-blockers (8 patients), sulfamethoxazole-trimethoprim (2 patients), aspirin (2 patients), and cimetidine (2 patients).
**PATIENTS AND METHODS**

The study population consisted of adult, nonalcoholic, nonepileptic patients (≥17 years old) with type 2 or type 1 diabetes mellitus. The patients were admitted to Rambam Medical Center, Haifa, Israel, between January 1, 1986, and December 31, 1992. This was a retrospective medical record review of diabetic patients who were admitted with DIHC or developed DIHC during hospitalization. Charts were reviewed for age, sex, medical history, diagnosis, results of laboratory tests, predisposing factors, use of potentiating drugs for hypoglycemia, complications, and outcome. **Hypoglycemic coma** was defined as a state in which the patient was not arousable (or responded only to pain), with a blood glucose concentration of 2.72 mmol/L (49 mg/dL) or less, and responded symptomatically (a return of consciousness) to the administration of intravenous glucose. Blood glucose levels were determined using the glucose oxidase method.

**Renal dysfunction** was defined either as creatinine clearance less than 1.33 mL/s (80 mL/min), as estimated from serum creatinine level, body weight, and sex according to the Cockcroft and Gault formula or serum urea nitrogen level greater than 9.25 mmol/L (25 mg/dL). **Chronic liver disease** was defined as any severe primary or secondary process that had been documented. A **risk factor** for hypoglycemia was defined as any medical condition or treatment found to be a potential causative factor for hypoglycemia.

Sixty-two patients responded to treatment during the first 12 hours, while 40 patients had protracted hypoglycemia of 12 to 72 hours’ duration. The estimated median duration of hospitalization because of DIHC was 2 days (range, 1-9 days). The morbidity related to the DIHC included physical injuries (head trauma in 4 patients and skeletal injury in 3 patients), seizures (8 patients), transient asymptomatic myocardial ischemia (manifested as rapid atrial fibrillation and ST-segment depression) (2 patients), and transient right hemiplegia (1 patient). Ninety-seven patients recovered and were discharged home or to an institution. Clinical notes were not sufficient to determine whether the patients had sequelae of hypoglycemic coma. Death occurred in 5 patients (4.9%). The clinical characteristics of these 5 patients are shown in the Table.

**COMMENT**

The brain is vitally dependent on glucose for its normal function and is able neither to store nor to synthesize glucose. Depletion of the supply of glucose to the brain rapidly causes impaired neuronal function, manifested by cognitive impairment or depression of level of consciousness, exhibited as obtundation, stupor, or coma. When the plasma glucose level declines below 2.77 mmol/L (50 mg/dL), appetite is increased and counter-regulatory hormones are released, initially glucagon and epinephrine and later cortisol, growth hormone, and norepinephrine, causing glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and proteolysis. Glucagon is the most important hormone for prompt recovery from acute hypoglycemia. Within 5 years of diagnosis, diabetic patients will demonstrate progressively impaired glucagon response in hypoglycemic states. Within 10 years of diagnosis, many will have impaired epinephrine responses, resulting in a loss of adrenergic symptoms. The combined loss of glucagon and epinephrine release results in greatly prolonged recovery from hypoglycemia.
The protracted hypoglycemia of 12 to 72 hours’ duration in 60.8% of our patients may be explained by the prolonged duration of diabetes and the concomitant risk factors for hypoglycemia. Severe hypoglycemia, defined as that associated with coma or requiring assistance of another person for reversal, occurs at least once a year in 10% of patients treated with insulin. It is listed as the cause or contributing factor for death in 3% to 6% of diabetic patients. This is more relevant to the elderly, because many become dependent on insulin treatment with time. There is increasing evidence that diabetes in many older patients that is initially controlled by diet or oral hypoglycemic agents and later requires insulin treatment is indeed type 1 diabetes mellitus, with positive islet cell antibodies.

A report that used both laboratory and historical assessment of hypoglycemia found a 20% incidence of hypoglycemia in sulfonamide-treated patients. Among our 102 patients with DIHC, the hypoglycemic coma occurred during hospitalization in only 3 patients. The actual incidence of DIHC in hospitalized patients is unknown. Fischer et al prospectively studied 42 hospitalized patients with diabetes mellitus who had a total of 64 episodes of hypoglycemia. In that study, insulin was implicated in 57 episodes (90%), but the number of patients with hypoglycemic coma was not mentioned.

In 1 prospective study of 125 patients seen in the emergency department with symptomatic hypoglycemia, coma was observed in 32 patients with blood glucose levels of 0.11 to 1.55 mmol/L (2-28 mg/dL). In our study, 48 patients had serum glucose levels below 1.72 mmol/L (31 mg/dL); however, DIHC occurred in 17 patients with blood glucose levels in the range of 2.27 to 2.72 mmol/L (41-49 mg/dL). This fact probably can be explained by associated conditions in elderly patients: compromised cerebral circulation, diminished cardiac output, or hypoxemia that could have contributed to the depressed sensorium. It also indicates the necessity to consider hypoglycemic coma as occurring at higher blood glucose levels than previously documented.

Age itself is an important factor in hypoglycemia. Among 842 patients aged 31 years or older with drug-induced hypoglycemia, 34% were older than 61 years. In our patients, age older than 60 years was a factor in 82.3%.

Restricted carbohydrate intake is one of the most frequent factors predisposing to drug-induced hypoglycemia. The duration of inadequate nutrition may range from missing only 1 or 2 meals to chronic starvation as might occur in patients with malignant neoplasms. In 35% of our patients, a history of low energy intake was obtained.

The association between hypoglycemia and renal insufficiency is more common than previously has been thought. Several mechanisms for the development of hypoglycemia during renal insufficiency have been proposed, including reduced renal gluconeogenesis and decreased energy intake. In normal subjects, renal gluconeogenesis may supply as much as 45% of new glucose during prolonged starvation. In a recent report, nearly 50% of hospitalized patients found to be hypoglycemic had chronic renal insufficiency. In our patients with renal dysfunction (68 patients [66.6%]), a concomitant decrease in food intake was also observed in 27 (26.4%). In these cases, renal compensation may not have been adequate.

Fourteen of our patients used drugs that were implicated as potentiating drugs for hypoglycemia by interacting with insulin or oral hypoglycemic agents, by competing for protein binding, or by interfering with renal excretion. Some of the drugs have additional hypoglycemic effects, such as aspirin, which stimulates muscle glucose uptake, and propranolol, which, in addition to masking the epinephrine-related early symptoms of hypoglycemia, inhibits muscle glycogenolysis and peripheral glucose utilization and blunts the glucagon response to insulin-induced hypoglycemia.

Most reports on 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, but...
rarely musculoskeletal injuries. Hepburn et al described serious musculoskeletal injuries in 6 patients during insulin-induced hypoglycemic convulsions. Seven of our patients had marked skeletal injury or head injury, and 8 patients had convulsion related to DHIC.

Fischer et al reported a 12% mortality rate among diabetic patients with hypoglycemia (90% were treated with insulin). However, hypoglycemia was not proved to be the cause of death in any patient. All the patients who died had serious secondary diseases, such as renal failure or sepsis. Hypoglycemia was more a marker of multisystem failure than the cause of death. Malouf and Brust reported a mortality rate of 11%, but only 1 death was attributable to hypoglycemia per se. Asplund et al reported that among 57 cases of glyburide-induced hypoglycemia, 10 patients fell into deep coma and died. Mortality among our patients was 4.9%, but it was impossible to conclude that hypoglycemia contributed to or caused the death of any patient, since all had serious secondary diseases.

CONCLUSIONS

Drug-induced hypoglycemic coma continues to be so common that virtually every unconscious patient should be considered hypoglycemic until immediate estimation of the blood glucose level rules it out. If hypoglycemia is confirmed, the clinician should promptly start 50% intravenous glucose and plan to maintain it uninterrupted for 1 or more days with added glucagon and hydrocortisone sodium succinate diazoxide if necessary, until all drug effects have worn off. It is difficult to compare the incidence of DHIC between different reports without uniform definitions of hypoglycemia, or similar ascertainment methods, patient populations, and levels of metabolic control. The benefits of tight control can be observed only between different reports without uniform definitions of hypoglycemia, or similar ascertainment methods, patient populations, and levels of metabolic control. The benefits of tight control can be observed only if it is implemented in appropriately selected patients. It has been demonstrated to achieve the goals of normalizing mean blood glucose level and reducing the risk of the development and progression of the microvascular and neurologic long-term complications of diabetes mellitus. Safe and effective treatment of diabetes mellitus, especially in the elderly, requires constant attention to comorbidities and other factors that interfere with insulin or sulfonylurea therapy. If this is not done, elderly patients are not different from the young in having the hazard of drug-induced hypoglycemia and the potentially serious complications associated with it.

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REFERENCES