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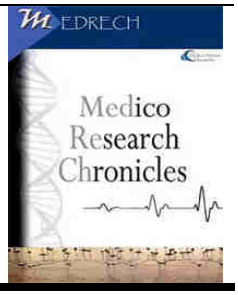

MAINTAINING NOCTURNAL GLYCEMIC STATUS USING INSULIN GLARGINE

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ARTICLE INFO **ABSTRACT** **REVIEW ARTICLE**

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INTRODUCTION

Hypoglycemia is a major limiting factor in achieving glycemic control in patients with diabetes. The American Diabetes Association recommends an HgA1C goal of less than 7% in most patients, and the American Association of Clinical Endocrinologists recommends an HgA1C less than 6.5%, if achievable without significant hypoglycemia. Landmark studies, such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Trial have clearly shown that tight glycemic control can prevent or delay the development of microvascular complications, such as retinopathy, nephropathy, and neuropathy, in type 1 and type 2 diabetes, but with aggressive glycemic targets comes an increase of hypoglycemia risk. Balancing strict glucose control to prevent microvascular and avoidance of hypoglycemia can become a challenge for both providers and patients[1]. Studies of glycemic control and diabetes complications before ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes to Prevent Vascular Disease), and VADT (Veterans Administration Diabetes Trial) indicate that severe hypoglycemia is less common with tight glycemic control in type 2 when compared with type 1 DM[2].

Hypoglycemia is defined as any glucose value low enough to harm a patient. Although no definite glucose value has been assigned to define hypoglycemia, as patients with diabetes may have different symptoms at various glucose levels, a glucose value less than 70 mg/dL should alert a patient or provider of possible impending hypoglycemia[1]. Results of the DCCT showed that intensive insulin therapy for a mean of 6 years (maintaining glycemic levels to a target hemoglobinA1c level of 7%), as opposed to conventional therapy (with resultant mean HbA1c level of 9%), significantly lowered the risk for retinopathy by 47%, for nephropathy

by 54%, and for neuropathy by 60%. On the other hand, episodes of hypoglycemia, especially at night, were common among people treated for type 1 diabetes, largely because usual insulin preparations do not adequately mimic the normal patterns of endogenous insulin secretion[3]. Risk factors for severe hypoglycemia include[2]:

(1) Prior to a severe hypoglycemia
(2) Hypoglycemia unawareness
(3) Defective insulin counter-regulation
(4) Age under 5 years
(5) Being elderly
(6) Certain co-morbid conditions such as renal disease, malnutrition, coronary heart disease, and liver disease.

Symptoms of hypoglycemia are usually divided into 2 main categories:

(1) Autonomic (sometimes called neurogenic or sympathoadrenal)
(2) Neuroglycopenic, which means related to deprivation of brain fuel

Normally, autonomic symptoms precede neuroglycopenic symptoms, that is, patients become shaky and sweaty before confusion sets in. A reversal of symptom order or loss of autonomic symptoms occurs in hypoglycemia unaware patients (part of the syndrome known as hypoglycemia-associated autonomic failure), whereas neuroglycopenic symptoms (related to fuel deprivation of the brain) may result in the inability to self treat[2].

Glucose provides fuel for energy, particularly the brain. The brain requires a continuous influx of glucose to function properly. Glucose is supplied exogenously, through ingested food, or endogenously, mostly stored in the liver in the form of glycogen. The kidneys play a role in glucose homeostasis, providing glucose through gluconeogenesis, and reabsorption of glucose through the proximal tubule. Normally, when plasma glucose levels fall, the body goes through a series of changes to increase glucose levels and maintain homeostasis. The first change, which occurs at glucose levels between 80 and 85 mg/dL is a decrease in insulin secretion from the pancreas. This is the first line of defense against hypoglycemia. This decrease in insulin increases hepatic and renal glucose production to increase overall glucose levels. The second line of defense occurs as glucose levels reach 65 to 70 mg/dL. At these glucose levels, glucagon is secreted from the pancreatic alpha cells into the hepatic portal vein. Glucagon stimulates hepatic glucose production through glycogenolysis. The third line of defense is the release of epinephrine, cortisol, and growth hormone, which also occurs at glucose levels in the range of 65 to 70 mg/dL. Epinephrine raises glucose levels through many mechanisms. It stimulates hepatic glycogenolysis and renal gluconeogenesis, suppresses insulin secretion from the pancreas, and increases glycolysis and lipolysis in muscle and fat. As glucose levels fall farther below 60 mg/dL, neuroglycopenic symptoms occur, prompting the patient to treat hypoglycemia by ingesting carbohydrate As glucose lowers below 50 mg/dL, cognition is altered. Prolonged very low glucose levels can cause brain death. In type 1 diabetes, this feedback mechanism is impaired. Patients with type 1 diabetes are insulin deficient, meaning the pancreatic beta cells do not produce insulin. These patients require exogenous subcutaneous insulin injections. When glucose levels drop, circulating insulin levels in patients with type 1 diabetes do not decrease as they would in patients with intact pancreatic function. These patients are also glucagon deficient. This results in loss of both the first and second lines of defense against hypoglycemia, predisposing these patients to more frequent and severe hypoglycemia. Patients with Type 1 diabetes are critically dependent on the third line of defense to combat hypoglycemia[1]. The type and doses of insulin prescribed are individualized per patient and are dependent on insurance preference, amount of injections per day, the motivation of the patient, willingness of the patient to inject insulin, degree of hyperglycemia, among others. Any patient who injects insulin is at risk of hypoglycemia.

Patients taking basal and bolus insulin (long-acting and rapid-acting insulins) require intensive glucose monitoring and multiple doses of insulin per day. The goal of the basal-bolus is to mimic physiologic insulin production. Prolonged fasting status, skipped meals, delayed meals, unfinished meals, or incorrect timing of insulin doses in relation to food can cause hypoglycemia. Patients who take premixed insulin, which contains both intermediate and rapid-acting insulin in one injection, are at higher risk of developing hypoglycemia if meals are skipped or inconsistent. Hypoglycemia frequently occurs overnight. It is the longest fasting period of the day, and insulin sensitivity increases between 1 AM and 3 AM. Patients may be unable to recognize hypoglycemia symptoms during sleep. Nocturnal hypoglycemia may cause rebound hyperglycemia on awakening. The importance of nocturnal hypoglycemia is difficult to overemphasize. Awareness of hypoglycemia is normally reduced during sleep. Nocturnal hypoglycemia can induce hypoglycemia unawareness and reduced insulin counter-regulatory defenses[2]. Renal, hepatic, or adrenal dysfunction can alter the response to hypoglycemia. In patients with renal dysfunction, medication clearance is slowed, prolonging the effects of medications such as insulin, sulfonylureas, and metiglinides. Patients with hepatic impairment may not be able to respond to hypoglycemia due to decreased glycogen stores. Patients with adrenal insufficiency are unable to respond to hypoglycemia because of impaired counterregulatory hormones. Elderly patients have a higher risk of hypoglycemia[1]. Recent work suggests that both uncontrolled hyperglycemia and repeated hypoglycemia may be risk factors for dementia in patients with diabetes[2].

Few strategies have emerged to reduce the frequency of nocturnal hypoglycemia—use of rapid-acting insulin analogs at dinner time, use of long-acting insulin analogs as basal therapy, and selective eating of bedtime snacks. Insulin lispro and insulin aspart are rapid-acting insulin analogs (also called rapid-onset and ultra-short-acting) that have been developed to target postprandial hyperglycemia. Because of the rapid onset of action, these insulin analogs can be injected before or even after meals, a property that benefits children and adults with unpredictable eating patterns. Because of their short duration of action, a slightly greater basal insulin supply may be needed when either of these analogs is used[4].

Mimicking the pancreatic ß cell increasingly accounts for the successful and safe management of insulin-treated diabetes. Physiologically, the ß cell essentially has 2 components of insulin output (Fig. 4). The first is a relatively constant level of insulin secreted between feeding periods to maintain euglycemia; this is the basal insulin and represents half or a little less of normal insulin secretion. There is a diurnal rhythm in basal insulin concentrations with a greater degree of insulin resistance in the early hours of the morning (dawn phenomenon) requiring increased insulin in some patients, especially younger ones. The second component of insulin replacement is adequate meal-related insulin secretion; this is the bolus insulin[2]. For many years, the most common insulin used to provide a basal insulin supply has been neutral (porcine) protamine Hagedorn (NPH) insulin, but this intermediate-acting insulin often results in nocturnal hypoglycemia due to unwanted plasma insulin peaks, particularly during the night, as well as higher fasting glucose levels. Insulin glargine (LANTUS) is a long-acting basal human insulin analog with a smooth time-action profile and no pronounced peak. Insulin glargine appears to mimic normal physiologic basal insulin concentrations more closely compared with currently available intermediate- and long-acting insulins[5]

In the case of insulin glargine, two arginine residues are added to the C-terminus of the B-chain and AsnA21 is replaced by Gly. This replacement increases the chemical

stability by avoiding deamidation of AsnA21, which is an issue, especially at low pH. The two Arg residues shift the isoelectric point from pH 5.5 to pH 6.7. Furthermore, the modifications optimize the packing density of insulin hexamers. Insulin glargine is formulated at pH 4.0, where it is soluble. After subcutaneous injection and mixing with interstitial fluid (pH 7.4), insulin glargine precipitates and the slow dissolution of insulin glargine from this subcutaneous depot together with the increased insulin glargine hexamer stability are the main reasons for the prolonged PK/PD profile. It has been previously assumed that the precipitate is microcrystalline, which could not be confirmed by analytical investigations of insulin glargine precipitates obtained in vitro and in vivo, however (Sanofi unpublished results). Upon dissolution from the subcutaneous depot, insulin glargine undergoes an enzymatic removal of the basic arginine pair and the resulting metabolite (GlyA21 human insulin) is the main active component, while there is virtually no parent glargine circulating in the plasma[6].

Meta-analyses of pooled data by Mullins et al. based on six studies in Type 2 diabetes, associated glargine with a 13.7, 39.3 and 53.7% risk reduction (all p <0.05) for symptomatic, confirmed and severe hypoglycemia, respectively, when compared with NPH insulin. The lower risk of hypoglycemia with glargine was apparent at all levels of HbA1c achieved, with a visible trend towards a greater difference at lower levels of HbA1c suggesting that individuals nearer target (HbA1c <8%) would experience the greatest reduction in risk[7]. A more recent meta-analysis has extended these findings to the risk of nocturnal hypoglycemia with glargine versus NPH insulin, in which the risk approximately halved with glargine (odds ratio = 0.44 for hypoglycemia with plasma glucose <2 mmol/l and 0.52 for hypoglycemia with plasma glucose <3.9 mmol/l). Based on this analysis, it was estimated that treating eight people with glargine instead of NPH insulin would prevent one person from experiencing a nocturnal symptomatic hypoglycemia event[7].

Betônico et al., compare the glycemic response to treatment with glargine U100 or neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes mellitus (T2DM) and CKD stages 3 and 4. Thirty-four patients were randomly assigned to glargine U100 or NPH insulin after a 2- way crossover open-label design. The primary endpoint was the difference in glycosylated hemoglobin (HbA1c) and the number of hypoglycemic events between weeks 1 and 24. After 24 weeks, mean HbA1c decreased on glargine U100 treatment (−0.91%; P < 0.001), but this benefit was not observed for NPH (0.23%; P ¼ 0.93). Moreover, the incidence of nocturnal hypoglycemia was 3 times lower with glargine than with NPH insulin (P ¼ 0.047). These results suggest that that insulin glargine U100 could be effective, once it improved glycemic control, reducing HbA1c with fewer nocturnal hypoglycemic episodes compared with NPH insulin in this population. These clinical benefits justify the use of basal insulin analogs, despite their high cost to treat patients with T2DM and CKD stages 3 and 4[8].

CONCLUSION

Insulin glargine is a long-acting insulin analog capable of providing 24-hour basal insulin coverage without pronounced peaks in insulin concentrations or activity. Structural modifications have created insulin that is solubilized in an acidic solution, but which crystallizes at the more neutral pH of the subcutaneous tissue, forming a depot from which the insulin is slowly released. Insulin glargine is administered once daily at bedtime. It has demonstrated efficacy comparable to that of NPH insulin administered once or twice daily in basal-bolus regimens with intermittent doses of regular insulin or insulin lispro in patients with type 1 and type 2 diabetes and in conjunction with oral antidiabetic agents in patients with type 2 diabetes. A reduced incidence of nocturnal hypoglycemia has been observed with the administration of insulin

glargine. Hypoglycemia is considered to be one of the major barriers to initiating insulin therapy and is often a deciding factor when selecting an insulin regimen. Therefore, it makes clinical sense to adopt a treatment regimen that minimizes this risk. Glargine has been shown to result in fewer hypoglycemic events than NPH insulin, along with comparable glycemic control.

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