

Insulin glargine

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Abstract: Insulin glargine is a long-acting human insulin analog prepared using recombinant DNA technology. It is the first long-acting analog of human insulin to be approved for clinical use. It is administered once daily and has a smooth 24 hour time-action profile that provides effective glycemic control with minimal risk of hypoglycemia. It may be used for children who are 6 years or older. Though the risk for developing hypoglycemia is less, hypoglycemia is still the most commonly reported adverse effect, especially within the first four weeks of therapy after a switching over to insulin glargine. Intravenous administration of this drug is not recommended due to the risk of severe hypoglycemia. The patients prescribed insulin glargine should be thoroughly counseled by the healthcare professionals regarding its safe and effective use. The vials and cartridges of insulin glargine should be stored in a refrigerator between 2 to 8 degrees C.

Keywords: Glargine, Hypoglycemia, Insulin.

Introduction

Insulin is a hormone produced by the beta cells of the islets of langerhans of the pancreas and consists of two amino acid chains.¹ Insulin is an anabolic hormone which mobilizes glucose from the blood to other areas of the body. It also helps the body to break down carbohydrates, fats and proteins from the diet. In Diabetes Mellitus (DM) patients will have either absolute (type 1 DM) or relative insulin deficiency (type 2 DM) wherein the pancreas does not produce enough insulin for the body's need.

The primary aim of insulin therapy is to replace endogenous insulin secretion in patients with type 1 or type 2 diabetes in a physiologically sound manner, mimicking the normal secretion pattern to adequately regulate glucose metabolism² and preventing long term complications of diabetes, such as coronary heart disease, nephropathy, neuropathy and retinopathy.³ Insulin is the mainstay for the treatment of virtually all type 1 DM and many type 2 DM patients. When necessary, insulin may be administered intravenously or

intramuscularly; however long term treatment relies on subcutaneous injection of the hormone.⁴ Recently, recombinant DNA technology has enabled production of insulin analogues with altered pharmacokinetic profiles like insulin lispro, insulin glargine and insulin aspart.

Chemical nature

Insulin glargine is a long-acting human insulin analog that is prepared using recombinant DNA technology and a special laboratory strain of nonpathogenic *Escherichia coli*.⁵ It is the first long-acting analog of human insulin to be approved for clinical use in the United States and Europe. Insulin glargine is produced by altering the human insulin molecule at two position, 21 of the amino acid chain and at the C-terminus of the B-chain which results in the formation of stable compound that is soluble at pH 4.0.⁶ This pH stabilizes the insulin hexamer and results in a prolonged and predictable absorption from subcutaneous tissues.^{4,7} There is also another once daily insulin called insulin detemir. This preparation is not available in Nepal and is not discussed in this article.

Insulin glargine

Indication

Insulin glargine is indicated for subcutaneous administration once daily at bed time in adults with type 1 diabetes mellitus or type-2 DM in patients who require long acting insulin for control of hyperglycemia. It is also indicated in pediatric patients aged ≥ 6 years with type 1 diabetes.⁸ In clinical studies, insulin glargine results in less hypoglycemia, has a sustained “peakless” absorption profile and provides a better 24 to 36 hours insulin coverage than ultralente or NPH insulin.

Therapeutic advantages

Insulin glargine is a long acting human insulin analogue which is administered once daily with a smooth 24 hours time-action profile that provides effective glycemic control with reduced hypoglycemia risk (particularly nocturnal) in patients with type 2 diabetes.⁹ It can be combined with various oral antihyperglycemic agents to effectively lower plasma glucose levels. Combination of glargine with sulfonylurea and/or Metformin can reduce both fasting (basal) and postprandial glucose levels.¹⁰

Pharmacokinetics

After subcutaneous injection, insulin glargine in healthy subjects and in patients with diabetes shows delayed absorption. Absolute bioavailability data are lacking.^{11,12} Absorption patterns are similar after subcutaneous injection into the arm, abdomen, or leg¹³ indicating lack of injection-site dependency.

Following a single 0.15 unit/kg dose in healthy subjects, a flat insulin profile between 1 and 24 hours was observed, with no pronounced peak. In contrast to insulin glargine, human isophane insulin (0.15 unit/kg) was rapidly absorbed; peak levels occurred within 3 hours, with a faster decrease toward preinjection values compared to insulin glargine.^{12,13}

Insulin glargine is partially metabolized by sequential cleavage at the carboxyl terminus of the B chain, to yield two active metabolites M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-thr-insulin) with similarity in structure and activity of human insulin. These degradation products are present both at the injection site and in plasma.^{14,15}

Mechanism of action

The primary action of insulin, including insulin glargine is regulation of glucose metabolism. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Dosage and administration¹⁶

Insulin glargine is administered by the subcutaneous route. Each milliliter (mL) of insulin glargine contains 100 international units (IU). A standard 100 unit insulin syringe can be used with this drug.

Adult Dosage

The normal dose in the case of type 1 DM, Insulin glargine may be administered at any time during the day and should be given subcutaneously once daily at the same time every day. Individualized insulin regimens should be developed for each patient based on self-monitoring of blood glucose (SMBG), patient motivation, and acceptance of insulin therapy. For patients with type 1 DM, dosage adjustments are usually not necessary when patients are transferred from once daily human NPH insulin or human ultralente insulin to insulin glargine. For patients previously treated with twice daily human NPH insulin, the initial dosage of insulin glargine should be reduced by 20% with adjustments based on patient response.

In case of diabetes mellitus type 2, the administration time of insulin glargine should be the same as that of type 1 DM. Individualized insulin regimens should be developed for each patient based on SMBG, patient motivation, and acceptance of insulin therapy. For patients with type 2 diabetes mellitus who are insulin naive and are being treated with oral antidiabetic drugs, the initial starting dose is 10 IU once daily, then adjusted based on SMBG. The total daily insulin dosage ranged from 2 to 100 IU.

Dosage in renal failure

Studies have not been conducted in patients with diabetes and renal impairment; however, the dosage of insulin glargine may be less in this population. Impaired renal function may result in reduced insulin metabolism as is the case with other insulins.

Dosage in hepatic insufficiency

Studies have not been conducted in patients with diabetes and hepatic impairment; however, the dosage of insulin glargine may be less in this population. Impaired hepatic function may result in reduced gluconeogenesis and insulin metabolism as is the case with other insulins.

Pediatric Dosage

Insulin glargine may be used in children who are 6 years or older; however, it has not been studied in children younger than 6 years of age. When patients are transferred from an intermediate or long-acting insulin to insulin glargine, the dosage may require adjustment. For patients who were

previously treated with twice-daily NPH human insulin, the initial dosage of insulin glargine was reduced by 20% and was subsequently based on patient response.

Comparative studies with other insulin preparations

A retrospective chart based study analyzed 114 children (n=60 aged 2 to 12; n=54, aged 13 to 18) with type I diabetes DM. All patients received continuous insulin therapies (NPH with regular insulin) for at least 1 year prior to starting insulin glargine in the evening and NPH during the day and had two or more HbA1c values greater than or equal to 8%. There was no difference in HbA1c from 6 months prior to 9 months after initiating insulin glargine therapy. Severe adverse events occurred in 22 of 114 (19%) patients prior to insulin glargine use (14 episodes occurred during the night) and in 9 of 114 (8%) patients during insulin glargine use (4 episodes occurred during the night).¹⁷

In a 28-week, multicenter trial, 264 and 270 patients with type 1 diabetes mellitus randomly received either insulin glargine or NPH human insulin, respectively. Patients treated previously with a daily injection of NPH insulin were switched on a unit-per-unit basis to insulin glargine; whereas, patients treated with twice daily NPH insulin received a slightly lower initial (decreased by 20%) dose of insulin glargine. The incidence of severe hypoglycemia after initial titration was significantly lower during treatment with insulin glargine versus NPH insulin. Insulin glargine and NPH insulin result in comparable glycemic control with a slightly lower incidence of severe hypoglycemia in patients treated with insulin glargine.¹⁸

In a multicenter, open-label, randomized, 24-week study, patients with type 2 DM for at least 2 years and treated with one or two oral antidiabetic agents for at least 3 months were included. All patients had a body mass index (BMI) between 26 and 40 kilogram/square meter (kg/m²), glycosylated hemoglobin (HbA1c) between 7.5% and 10%, and fasting plasma glucose (FPG) greater than or equal to 140 milligrams/deciliter (mg/dL). Patients were randomized to receive either insulin glargine (n=367) or human NPH insulin (n=389) administered subcutaneously at bedtime. Patients continued their oral antidiabetic regimen. The rates of hypoglycemia, expressed as events per patient year, were 13.9 for insulin glargine and 17.7 with insulin NPH (p less than 0.02).¹⁹

When used in combination with fixed-dose oral therapy (glimepiride 3 milligrams/day) for inadequately controlled type 2 diabetes, morning injection of insulin glargine provided better glycemic control than either a nighttime dose or bedtime NPH insulin. Nocturnal hypoglycemic episodes occurred in 17% and 23% of patients given once

daily morning or evening doses of insulin glargine, respectively, compared to 38% of those given bedtime NPH insulin (p less than 0.001 for both).²⁰

Adverse effects²¹

Hypoglycemia is the most commonly reported adverse effect, especially within the first four weeks of therapy after a switch to insulin glargine.²² Other ADRs include cutaneous hypersensitivity, pain at the injection site, rash and lipodystrophy. Serious ADRs like hypoglycemia can also occur.

Drug interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and close monitoring. The drugs that may increase the risk of hypoglycemia are oral antidiabetics, ACE inhibitors, disopyramide, fibrates, fluoxetine, mono amine oxidase inhibitors, propoxyphene, salicylates and somatostatin analogs (e.g. octreotide).

Contrary to the hypoglycemic effects, some drugs may suppress the hypoglycemic effects of glargine. These drugs include corticosteroids, danazol, diuretics, sympathomimetic agents (e.g. epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g. oral contraceptives).

A few drugs like beta blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.^{23, 24}

Precautions

Insulin glargine is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on delivery to the subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. If insulin glargine is diluted or mixed with any other insulin product or solution the preparation may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g. onset of action, time to peak effect) of the mixed insulin may be altered in an unpredictable manner.^{24, 25}

Contraindications

Hypersensitivity to any component of insulin and intravenous administration of this drug is not recommended due to development of severe hypoglycemia. Insulin glargine should not be used to treat diabetic ketoacidosis.

Warnings

Hypoglycemia is the most common adverse effect of insulins

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including glargine. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended in all patients with diabetes. Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g. regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.⁵

Use in special populations

The effects of renal or hepatic impairment on the pharmacokinetic of insulin glargine in patients with diabetes mellitus have not been evaluated. However, increased circulating concentration of insulin has been observed in patients with renal or hepatic impairment who were receiving human insulin; therefore, insulin glargine requirements may be reduced in these patients. Careful monitoring of blood glucose and adjustment of insulin glargine dosage may be necessary in such patients. Safety and efficacy is not established in children younger than 6 years of age. In case of geriatric patients initial dosage, dose increments and maintenance dosage should be conservative to avoid hypoglycemia.⁵

Advice to patients^{26,24}

The patients on insulin glargine should be provided counseling. Some of the points to be counseled are listed below.

1. Insulin glargine should be administered subcutaneously once a day at the same time every day. It should never be administered by intravenous route
2. It should not be diluted or mixed with any other insulin or other solutions. The syringe used to administer insulin glargine must not contain any other medicinal product or residue inside it
3. In case of insulin pen delivery device malfunction, the injection may be drawn from the cartridge system into a U-100 syringe and injected
4. It should not be refrigerated opened (in-use) cartridge when installed in the delivery device
5. Any insulin that is discolored, looks thick, has particles in it, or looks different from previous bottles, cartridges or pens should not be used
6. The patient should be advised to change the injection

sites. Usually, the patient should not inject within 1 inch of the same site within one month.

7. The patient should not change the insulin strength (e.g. U-100) or insulin type (e.g. glargine, lispro, Regular etc) unless recommended by the doctor
8. The patient should not change the brand of insulin glargine or syringe without talking to the doctor.
9. Once punctured, the insulin vial in use, whether stored in the refrigerator or at room temperature, must be used within 28 days.
10. Alcohol may cause a decrease in blood sugar leading to hypoglycemia. The patient should be encouraged to ask the doctor about the safe use of alcoholic beverages while using insulin glargine.

Storage condition²⁷

Insulin glargine (vials and cartridges) should be stored in a refrigerator between 2 to 8 degrees C. This product should not be frozen. The 10-mL vial or cartridge that is being used can be stored unrefrigerated as long as the temperature does not exceed 30 degrees C. The opened vials or cartridges should be used within 28 days. For patients using insulin pens, the product should not be refrigerated once the cartridge is placed in the device.

Availability

Insulin glargine is available in the form of injection 100 unit/mL in 10 mL vial. Recently, the drug has been approved and is available in Nepal.

Pregnancy category

The United State Food and Drug Administration (US FDA) has classified insulin glargine under the pregnancy category 'C'. Category 'C' means, either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. The drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Conclusion

Insulin glargine being long acting insulin has got some major advantages. The most important advantage is convenient once daily dosing. Its delayed onset and prolonged, flat time-action profile mimic the action of endogenous basal insulin (or an insulin pump), decreasing the risk of hypoglycemia. It may be a useful new option for meeting overnight insulin requirements, although most patients will require rapid-acting insulin such as insulin lispro

either with or before meals for optimal management of blood glucose levels. This can definitely improve patient compliance and can provide a better glycemic control.

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