Brief Communication

High Concentration Insulin

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Abstract

This communication reviews available high concentration insulins and their basic as well as clinical pharmacology. It classifies all high concentration insulins, and describes their pharmacokinetic and pharmacodynamic properties. The article discusses the utility of high concentrations insulins, lists indications for these preparations, highlights caveats for their safe use, and proposes pragmatic contraindications to their prescription.

Keywords: U200 degludec, U200 lispro, U300 glargine, U500 regular insulin, ultralong acting insulin

Introduction

Along with the increase in the number of persons living with diabetes, other challenges are also being noted. While there is an increase in the number of insulin prescriptions, the dose requirement of insulin also shows an upward trend. Increasing body weight, and worsening insulin resistance, both contribute to higher insulin doses. In some individuals, existing insulin preparations and delivery devices, which have limited maximal dosage delivery may not suffice. To meet this challenge, concentrated insulin has been developed. This review describes the various concentrated insulin that are available worldwide and discusses evidence, indications, caveats, and precautions for their use.

Classification

At least seven high concentration preparations have been developed so far (2017). These include degludec U200 (Novo Nordisk), glargine U300 (Sanofi), lispro U200 (Eli Lilly), and regular insulin U500 (Eli Lilly). U200 regular insulin, NPH insulin, and 30:70 insulin are also manufactured by Wockhardt. The details of these insulin are mentioned in Tables 1 and 2. While high concentration, degludec retains the ultra-long characteristics of U100 degludec, glargine U300 is classified as ultra-long acting, as opposed to the long-acting nature of U100 glargine. Similarly, U200 lispro shares the same pharmacokinetic and pharmacodynamic (PK/PD) properties of U100 lispro, but U500 regular insulin has totally different pharmacokinetic properties as compared to U100 regular insulin [Table 1]. Not much detail is available about the U200 human insulin in published literature.

Insulin Degludec U200

Insulin degludec U200 (IDeg U200) concentration is designed to allow the administration of up to 160 units of IDeg in a single injection. This helps reduce injection volumes for patients with large insulin requirements (>80 U/day) which cannot be administered by a single injection with the U100 pen. During its development, the U200 formulation was optimized with a slight adjustment of the excipients to obtain the same pharmacological properties and effect as U100. A double-blind, crossover, randomized, comparative study was done in 33 type 1 diabetes mellitus patients under steady state conditions to demonstrate the PK/PD properties between the two IDeg formulations (U100 and U200). IDeg U200 was found to be bioequivalent and had similar pharmacodynamic profiles as IDeg U100, implying that they can be used interchangeably in clinical practice.[1] Similar results were seen in BEGIN COMPARE trial done in 373 participants with type 2 diabetes. IDeg U200 was shown to provide effective glycemic control while maintaining a low rate of hypoglycemia, similar to IDeg U100.[2] The above

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Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_300_17

How to cite this article: Kalra S. High concentration insulin. Indian J Endocr Metab 2018;22:160-3.

results confirm that the two formulations of IDeg show similar pharmacological properties and are clinically equivalent. Therefore, the frequency, technique, and dosage of IDeg U200 are similar to that of IDeg U100.[3]

Glargine U300

Glargine U300 is a next-generation basal insulin with a novel formulation of insulin glargine. Glargine U300 has a more constant PK/PD profile with a prolonged duration of action beyond 24 h. As a result, in a single-dose glucose clamp study, blood glucose-lowering activity was maintained for up to 36 h with glargine U300 dosed at 0.4, 0.6, and 0.9 U/kg. At steady state, glargine U300 provides a more constant and more evenly distributed insulin concentration profile and GIR profile over 24 h than glargine U100. Glargine U300 provides an evenly distributed 24 h coverage, as a result of low fluctuations (within-day variability) and high day-to-day reproducibility in insulin exposure.[4-6]

Insulin glargine U300 has been evaluated in a comprehensive series of randomized controlled trials in patients with type 1 and type 2 diabetes, termed EDITION. In the six studies, Glargine U300 consistently showed comparable glycemic control to Glargine U100.[7-14]

In addition, both in patients with type 1 and type 2 diabetes, glargine U300 reduces the risk of hypoglycemia. In a meta-analysis of the Phase 3 trials, glargine U300 was associated with reduced nocturnal and anytime hypoglycemia compared with glargine U100, with a relative risk of 0.75 (95% confidence interval: 0.68–0.83) and 0.91 (95% CI: 0.87-0.96), respectively.[15,16]

The improved PK/PD properties of glargine U300 thus translate into important clinical benefits such as prolonged glucose control from a once-daily dose, a more even activity profile, a reduced risk of nocturnal hypoglycemia, and more flexibility in the dosing interval.

U500 Regular Insulin

High-dose U500 regular insulin demonstrates both short-acting prandial and long-acting basal activity. As compared to U100 regular insulin, it has a similar time to effect (<20 min), a lower peak concentration, a longer time to maximal effect (6 h and 5 h), and greater duration of action (24 h and 18 h) in doses of 0.4–0.6 U/kg (50 U) and 0.8–1.3 U/kg (100 U). In contrast, U100 regular insulin demonstrates a time to peak effect of 3 h and a duration of action of 8 h.[17-21]

The U500R titration-to-target randomized controlled trial proved equivalent HbA1c reduction with U500 regular insulin in both twice daily and three daily regimens. The incidence of severe hypoglycemia was low, whereas weight gain was modest. Nonsevere hypoglycemia was less in the thrice-daily arm. Patient reported outcomes were positive.[17,18]

At the same time, due diligence must be practiced while selecting patients for U500 regular therapy.[19,22] Red flags (i.e., potential or relative contraindications) include poor adherence, hypoglycemia unawareness, high risk of age, cognitive/psychiatric impairment, and inability to take regular meals. U500 regular insulin should not be administered with other insulin preparations as it covers both prandial and basal needs. Noninsulin-sensitizers and incretin-based therapies may be considered in combination, as per clinical requirement.

To transition from high-dose volume U 100 insulin to U500 regular insulin, one should reduce the total current dose by 20%. U500 regular insulin can be prescribed twice daily in a 60:40 am:pm ratio or a 40:30:30 three meal based ratio.

Table 1: Classification of high concentration insulin

Type of insulin	PK/PD profile*	
	Distinct	Similar
Short acting	U500 regular insulin	U200 lispro; U200 regular insulin
Long acting	U300 glargine	U200 degludec; U200 NPH insulin
Premixed		U200 30:70 insulin

*As compared to U100 version. PK/PD: Pharmacokinetic/pharmacodynamics

Table 2: Pharmacologic characteristics of high concentration insulin

Concentrated insulin	U200 degludec	U300 glargine	U200 lispro	U500 regular insulin
Type of insulin	Basal analogue	Basal analogue	Regular analogue	Basal + prandial combined
U-100 comparator	U100 degludec	U100 glargine	U100 lispro	U100 regular
Delivery device	Prefilled pen (3 mL)	Prefilled pen (1.5 mL)	Prefilled pen (3 mL)	Prefilled pen (20 mL); vial (30 mL)
Maximum dosage	160U	80U	120U	300U; 250U
Minimum increment	2U	1U	1U	5U; 5U
Timing of admin	Per EU label, any time of the day, preferably at the same time every day	Per EU & Indian label, any time of the day, preferably at the same time every day	With meals	30 min before meals 2-3 times/day
Efficacy*	Similar	Similar	Similar	Greater
Variability*	Less	Less	Similar	Less
Duration of action*	Similar	Greater	Similar	Greater
Risk of hypoglycemia*	Similar	Less	Similar	Greater
Risk of nocturnal hypoglycemia	Similar	Less	Similar	Greater

*As compared to U100 version

Table 3: Indications and potential indications for U500 regular insulin

Indications
Severe insulin resistance
High insulin requirement
Refractory diabetes
Dissatisfaction with basal-bolus regime/multiple injections
Contraindications
Biomedical
Extremes of age
High risk of hypoglycemia
Cognitive impairment
Hypoglycemia unawareness
Debilitated state
Psychosocial
Irregular/erratic/extreme meal patterns
Inability/unwillingness to self-monitor
Poor adherence to therapy
Poor self-care habits
Psychiatric impairment

The choice of initial injection frequency usually will depend on patient acceptance, rather than on biomedical concerns, including postlunch glucose values. Thrice-daily U500 insulin may be needed in persons who have a high lunch hyperglycemia, predinner hyperglycemia, or develop nocturnal hypoglycemia. Posttransplant patients may benefit from a thrice-daily regimen as well.

Frequency of follow-up, whether telephonic or in person, may vary from practice to practice. However, weekly or biweekly contact must be ensured for the first few weeks. Doses of U00 regular insulin are titrated so as to target preprandial glucose values before the subsequent meal, for example, the breakfast dose targets predinner glycemia. In this context, use of U500 regular insulin is similar to that of premixed insulin.

U200 Lispro

U200 Lispro maintains the same PK/PDs properties that U100 Lispro exhibits. As it's concentration is double that of U100, it can be injected in doses of up to 120 units [as opposed to 60 U for U100 lispro], using a disposable pen device.[23]

Utility

Concentrated insulin can be used in all persons who require insulin therapy. It must be noted that the order of clinical decision-making should be as follows: decide upon insulin therapy, then choose the optimal insulin regimen, identify the appropriate insulin preparation, and then prescribe the right insulin concentration. Specific indications and contraindications are mentioned in Table 3.

Concentrated basal insulin can be prescribed as an alternative to U100 basal insulin. These insulin will offer the advantages of low injection volume, leading to less pain, and low variability, leading to lesser risk of hypoglycemia. U 300 glargine will provide ultra-long-acting coverage, thus allowing better fasting glucose control. The concept of basal insulin dissimilarity can, therefore, be expanded to insulin concentration dissimilarity. Specific clinical situations where U300 glargine may be preferred over U100 glargine include dawn phenomenon, Somogyi phenomenon, and brittle diabetes.

High concentration short-acting insulin can be used in persons who require high doses of insulin (i.e., have severe insulin resistance). Persons who are not well controlled on multiple doses of basal or premixed regimes, or who wish to reduce the number of injections per day, may benefit from U500 regular insulin. Although U500 is a regular insulin, it possesses both prandial and based glucose-lowering activity and may work in a manner similar to premix insulin.

Caveats

As with all insulin, proper insulin technique is a must for concentrated insulin. U 200 degludec, U300 glargine, and U200 lispro are marketed in devices which are similar to those of their U100 versions. Hence, the method of administration will remain the same. U500 regular insulin is marketed as prefilled pens and vials. The U500 regular insulin vials must be used with U500 insulin syringes, which have a green cap, and allow the maximal dose of 250U, in increments of 5 U. The method of injection is the same as that of U40 and U100 syringes.

Summary

Patient, as well as provider education, is of utmost importance, to prevent errors in prescription, dispensing, and administration. The entire health-care team, including a physician, pharmacist, educator/nurse, patient, and support providers, must be aware of the concentration of insulin being used. If utilized properly, high concentration insulin can offer efficient and effective glycemic control to persons requiring high doses of insulin, in a safe and well-tolerated manner.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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