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When Should I Use Newer Insulins?

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KEYWORDS

Insulin analogues, newer insulins, hypoglycaemia, variability, flexibility

BACKGROUND

Diabetes is a major public-health problem that is globally reaching epidemic proportions, affecting 415 million people worldwide[1]. Insulins remain the cornerstone of treatment in type 1 diabetes and also in later stages of type 2 diabetes (T2D). If uncontrolled, diabetes can lead to a myriad of microvascular and macrovascular complications, culminating in premature death. Hence, compliance with therapy is important to prevent the adverse clinical effects of the disease[2].

Since its discovery in 1921, insulin preparations have been continually evolving and improving. From animal insulins (bovine and porcine) to human insulin in the late 1940s, research was continuously ongoing due to an increased demand for the same. Further milestones were the introduction of insulin analogues in the 1990s, initially rapid-acting followed by the long-acting basal analogues in 2000s. And now, we have reached the era wherein the possibility of oral insulin is not too far ahead in the future[3].

During the past few decades many manipulations of the insulin molecule have been attempted, in an effort to provide an effective and safer treatment option for patients. The newer insulins have been formulated to allow for a closer replication of a normal insulin profile[4].

Despite improvements in both basal and prandial insulin, a number of challenges still remain. Hypoglycemia remains the greatest challenge; it prevents many from achieving optimal glycaemic control, and nocturnal hypoglycemia is feared by many. Missed injections and mistimed injections also pose a problem for many, due to less flexible regimens. Table 1 gives the pharmacokinetics & pharmacodynamics of newer insulins.

Table 1: Key PK/PD data of available insulins in India[5]

Name	Type	Onset (min)	Peak (hrs)	Duration (hrs)
Human Insulins				
Regular Human Insulin (RHI)	Short-acting (Prandial)	30 – 60	2 – 3	5 – 8
Biphasic human insulin (BHI) 30/70	Premixed	30 – 60	Dual	10 – 16
Biphasic human insulin (BHI) 50/50	Premixed	30 – 60	Dual	10 – 16
Neutral Protamine Hagedorn (NPH)	Intermediate-acting (Basal)	120 – 240	4 – 10	10 – 16
Modern Insulins				
Aspart	Rapid-acting (Prandial)	5 – 15	0.5 – 1.5	< 5
Lispro	Rapid-acting (Prandial)	5 – 15	0.5 – 1.5	< 5
Glulisine	Rapid-acting (Prandial)	20	1.5	5.3
Biphasic Insulin Aspart (BIAsp) 30/70	Premixed	5 – 15	Dual	10 – 16
Biphasic Insulin Aspart (BIAsp) 50/50	Premixed	5 – 15	Dual	10 – 16
Lispro Mix 25/75	Premixed	5 – 15	Dual	10 – 16
Lispro Mix 50/50	Premixed	5 – 15	Dual	10 – 16
Glargine	Long-acting (Basal)	120 – 240	No pronounced peak	Up to 24
Detemir	Long-acting (Basal)	48 – 120		Up to 24
Degludec	Ultra Long-acting (Basal)	30 – 90	Peakless	> 42
Degludec/Aspart (IDegAsp)	Co-formulation	5 – 15	0.5 – 1.5	> 24

An ideal basal insulin would have a flat-time action profile with minimal day-to-day variability. A better rapid-acting insulin would further improve postprandial glucose levels as well as have a shorter time-action profile to avoid late hypoglycaemia, but long enough so that the between-meal glucose levels do not rise too high[6].

LIMITATIONS OF CONVENTIONAL INSULINS[3]

- Onset: delayed
- Advised to inject 30 min before meals – makes the regimen less flexible.
- Less insulin increase in early phase of glucose absorption → excessive rise in glucose at 1-2 hrs after meal.
- At 4-5 hrs after subcutaneous injection, inappropriate hyperinsulinemia → hypoglycaemia.
- Defensive snacking, in between meals, to counter hypoglycaemia → weight gain.
- Glycaemic variability.
- Dose has a profound effect on time action profile.

WHEN CAN I USE NEWER INSULINS?

Newer insulin analogues can be used to advantage, in a subset of patients with diabetes.

Hypoglycaemia / Recurrent Hypoglycaemia /Hypoglycaemia Unawareness

Fear of hypoglycaemia and its associated risks of accident, coma, or death remains a major obstacle to the pursuit of good glycaemic control[7]. In general, all insulin analogues have shown lower rates of overall, major and nocturnal hypoglycaemia compared to human insulins.

Newer insulins have a distinct advantage in those patients who have experienced 1 or more hypoglycaemic episodes on their current regime and in those who have hypoglycaemia unawareness.

In a recently conducted study, 22% of Indian patients have deliberately not dosed their insulin as prescribed & 23% let blood glucose (BG) levels go higher to reduce their risk of nocturnal self-treated hypoglycaemia[8].

The Cochrane review of rapid-acting insulin analogues vis-à-vis regular human insulin found a lower incidence of severe hypoglycaemic episodes. Individual trials have also reported lower rates of overall, major and nocturnal hypoglycaemia[9]. Similarly, the Cochrane review of the basal insulin analogues vis-à-vis NPH found significantly lower risks of nocturnal, symptomatic as well as severe hypoglycaemia with glargine and detemir[10].

A pre-specified and planned meta-analysis of the phase 3 trials of insulin degludec vs. insulin glargine, showed a 38% reduction in nocturnal hypoglycemia overall in T2D, and 49% in insulin-naïve patients[11]. This was further corroborated by the SWITCH-2 trial, which showed 30% and 42% significant risk reduction of severe or BG confirmed symptomatic and nocturnal hypoglycaemia respectively[12].

Less Weight Gain

It is presumed that weight gain is an inevitable consequence of insulin therapy[13].

With the advent of insulin analogues which have demonstrated lesser hypoglycaemic episodes, defensive in-between meal snacking is reduced which leads to less weight gain.

Various trials, with insulin degludec, have reported lesser dose required at the end of the trial, compared to its comparators, as reported in a meta-analysis of the phase 3 trials. Lesser insulin dose requirement would also translate into lesser weight gain[14].

A meta-analysis of trials of insulin detemir showed there was significantly less weight gain compared to insulin glargine, despite similar glycaemic control and risk of hypoglycaemia. This weight-sparing effect appears to be unique to insulin detemir[13].

Glycaemic Variability

Glycaemic variability predicts hypoglycaemia and has consistently been related to mortality even in non-diabetic patients. Day-to-day variability of insulin effects could have deleterious consequences and may hamper proper management[15].

Insulin detemir and glargine have demonstrated 28% and 48% intra-patient variability, respectively, compared to the 68% with NPH[16].

Insulin degludec has gone a step further and demonstrated 75% lesser intra-patient variability vis-à-vis insulin glargine, both U100 and U300[17]. With U100, this was further corroborated in a Japanese study, using continuous glucose monitoring, which showed higher variability with insulin glargine with a significant amount of time spent in hyperglycemia[18].

With a flatter and more predictable action profile, the requirement of SMBG also reduces, which is an advantage for those who have difficulties in performing frequent SMBG.

Flexible Timing of Administration

Flexibility of an insulin regime or preparation can be defined as their ability to be injected at variable times, with variable injection-meal time gaps[19].

All insulin analogues offer the advantage of meal time flexibility, i.e. can be taken at the beginning of the meal or even upto 15 mins of starting the meal, as opposed to conventional insulins which need to be injected 30 min before start of the meal[2].

The Indian cohort of the GAPP (Global Attitudes of Patients and Physicians in Insulin Therapy) study has reported that 2-in-5 patients had missed a dose of basal insulin within the last 30 days[8].

Glargine can be injected at any time of the day, at the same time each day. Insulin degludec can be injected at any time of the day, without regards to the previous

Table 2: Newer insulins in the pipeline

Basal Insulin	Prandial Insulin	Available outside India
Glargine U300	Insulin PH20	Degludec U200
	Linjeta	Inhaled insulin (Afrezza)
	Faster acting insulin aspart	

injection timing, provided an 8 h gap is maintained, and upto 40h should a dose be missed[19].

Special Situations

- Pregnancy

  Given the importance of excellent glycaemic control in pregnancy and the problem of hypoglycaemia, insulin analogues may offer potential benefits in pregnant women with diabetes.

  Amongst the rapid-acting analogues, insulin lispro and aspart are safe in pregnancy and may improve post-prandial glycaemic control.

  Insulin detemir has shown improved fasting glucose compared to NPH, without an increased incidence of hypoglycaemia[20].

  All these 3 insulins are approved and are classified as Category B drugs for use in pregnancy.

- Elderly

  Recurrent hypoglycaemia is common in older people with diabetes. It is less recognized and usually under-reported. Hypoglycaemia is associated with significant morbidities, more so in the elderly, as it can lead to both physical and cognitive dysfunction[21].

  If insulin therapy is required, then this subset of patients may benefit from the newer insulins, as they have reports of significantly lesser hypoglycaemic episodes, especially nocturnal hypoglycaemia.

- Children

  Insulin analogues have a distinct advantage in children. They offer meal-time flexibility (this is not only effective for good glycaemic control but also helps combat erratic children behaviour, for children who are reluctant to eat) and reduced rates of hypoglycaemia[22].

  Amongst the rapid-acting analogues, insulin aspart can be used for children >2 years, lispro for >3 years and glulisine for >6 years. Amongst the basal analogues, insulin glargine can be used for children > 2 years and detemir for > 1 year.

Intensification

At some point after initiation of therapy with basal insulin, it will no longer be enough and increasing the basal dose alone will be inadequate. At that point, addition of mealtime coverage will be needed to address the postprandial levels[23].

Conventionally, after basal failure the options to intensify therapy are by adding a shot of prandial insulin to the largest meal or switching to premixed insulin.

At this point, IDegAsp offers the convenience of a "basal-plus" regimen, in a single device.

IDegAsp is a novel co-formulation of basal insulin degludec (IDeg) and rapid-acting insulin aspart (IAsp) (ratio 70% IDeg: / 30% IAsp), available as a single subcutaneous injection.

The clinical trial program of IDegAsp has demonstrated comparable glycaemic efficacy and similar hypoglycaemia rates compared with standard basal–bolus treatment, with fewer shots and two different insulins in the same device.

In comparison to premixed analogues, IDegAsp provided effective reduction in HbA_1c comparable with BIAsp30, with superior reductions in FPG levels[24]. A subsequent combined analysis has also demonstrated lower overall rates of confirmed and severe hypoglycaemia, and a significantly lower rate of nocturnal hypoglycaemia, with twice-daily IDegAsp vis-à-vis BIAsp30[25].

EXAMPLES OF PATIENT PROFILES WHO MAY BENEFIT FROM NEWER INSULINS[19]

- Persons with erratic meal timings
- Persons with irregular exercise schedules
- Those who have a busy lifestyle, who cannot inject at the same time every day
- Those who depend on others for assistance in insulin injection
- Those who cannot monitor blood glucose frequently
- Shift workers
- Those who travel frequently, warranting a change in time zone.

FUTURE INSULINS AND DELIVERY SYSTEMS (TABLES 2 & 3)

Continued progress in the field of newer insulins is on as well with research extending to developing other routes of insulin administration.

The concept of a smart insulin involves an insulin that would be responsive to the existing plasma glucose levels and would work more effectively when glucose levels are high and less effectively when glucose levels are lower[5].

Continuous Subcutaneous Insulin Infusion (CSII) is emerging as the gold standard akin to the artificial pancreas. Steady progress is being made towards this, which will ultimately be a fully automated, closed-loop, glucose control system comprising a continuous glucose monitor, an insulin pump, and a controller. Although glycaemic efficacies in CSII are similar, safety data show lower pump occlusion rates with insulin aspart (9.2%) compared with lispro (15.7%) and glulisine (40.9%)[27].

Table 3: Alternative routes of insulin administration[26,27]

Route	Advantage	Disadvantage
Pulmonary/ Inhaled	• High permeability • Large surface area • Rich vasculature • Lack of mucociliary clearance • Immunotolerance	• Low bioavailability (9 – 22%) • Variation in absorption • Large quantity insulin required • Cannot be used by smokers. • Mild to moderate cough, shortness of breath, sore throat, dry mouth
Oral	• Easy and convenient • Patient compliance • Easily accessible route	• Low bioavailability (1%) • Proteolytic degradation in GIT. • First-pass hepatic metabolism • Large quantity insulin required • High resistance by intestinal epithelial barriers
Transdermal	• Large surface area • Micro-needle approach increases insulin permeability. • Can use iontophoresis & sonophoresis techniques	• Skin is impermeable • Variability in dosing
Nasal	-Large absorptive surface -High vascularity	• Low bioavailability (8-15%) • Degraded by proteolytic enzymes • Nasal irritation • Nasal tolerance • High rates of treatment failure • Mucociliary clearance • Inconsistent absorption
Ocular	• Fast systemic absorption • No first-pass hepatic metabolism	• Low bioavailability • Local irritation
Rectal	• Avoids local enzymatic degradation • Insulin enters systemic circulation via the lymphatic system. • No first-pass hepatic metabolism	• Local adverse reactions • Low and variable levels of absorption • Local irritation
Buccal	• No first-pass hepatic metabolism • Good accessibility • Drug is in direct mucosal contact, • Avoids acidic pH of stomach • Large surface for absorption • High vascularity • Quite robust • Improved compliance	• No first-pass hepatic metabolism • Good accessibility • Drug is in direct mucosal contact, • Avoids acidic pH of stomach • Large surface for absorption • High vascularity • Quite robust • Improved compliance
Patch Pad[25]	• Ease of use, accuracy • Predictability • Ability to calculate bolus insulin doses based on user-input	• Temporary unavailability of a controller device • Pump size (form factor) • Adhesive intolerance • Poor adherence

For many patients, administering insulin by subcutaneous injection seems like a daunting therapy option. Consequently, research is being undertaken on alternative methods for administering insulin. An ideal route for insulin delivery should have the ability to provide effective and predictable lowering of blood glucose level.

Continuous subcutaneous insulin infusion (CSII), popularly known as the 'insulin pump' provides a precise and controlled rate of insulin delivery to diabetic patients who would normally need multiple daily injections to regulate blood glucose levels. The main benefit of insulin pump therapy is the flexible and accurate basal and bolus

dosing to meet patient's individual insulin requirements while reducing the risk of severe hypoglycaemia.

SUMMARY

The advent of newer long-acting analogues with more physiological basal profile holds promise, as does the new co-formulation with the convenience of a "basal-plus" regime in a single device. Additionally, it has be to kept in mind, that human insulins may have a modestly higher projected cost as the impact of hypoglycaemia is not accounted for.

Newer insulins, although expensive, offer some distinct advantages over existing ones. They reduce the rates of hypoglycaemia (especially nocturnal hypoglycaemia), have lower levels of postprandial glucose excursions (for the rapid acting analogues), better patient adherence, greater quality of life, and higher satisfaction with treatment. They offer flexibility in daily dosing and have the added advantage of reduced glycaemic variability.

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