Addressing Barriers to Effective Basal Insulin Therapy

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Abstract

Diabetes has reached epidemic proportions worldwide. It is a major health hazard particularly in developing countries like India due to the genetic susceptibility and changes in lifestyle. Glycaemic control is very poor in India as reflected by recent studies showing average HbA1c of > 9%.

Insulin therapy is the mainstay of diabetes management. Currently available insulins have certain limitations. Modern insulin therapy needs to overcome these limitations to effectively achieve the optimal glycemic control. Hypoglycaemia is one of the important barrier which limits the use of insulin therapy and incidence of hypoglycaemia increases with increased variability in glucose lowering effects of Insulin when one tries to achieve stricter glycaemic targets. Fixed time administration is another important barrier, particularly for basal insulin administration that may affect the quality of life. Also the available basal insulins do not provide complete 24 hours control of fasting hyperglycaemia.

Insulin degludec is designed to have a flat and stable glucose-lowering effect for more than 42 hours with less risk of hypoglycaemia. And it overcomes most of the issues with currently available basal insulins.

Introduction

Diabetes is a global epidemic with an estimated 371 million individuals currently living with this disease. By 2030, this number is projected to reach 552 million or 9.9% of the adult population.[1] The ICMR-INDIAB national diabetes study reported a total of 62.4 million patients with diabetes and 77 million people with pre-diabetes in India.[2] Recently published results of A_1chieve study have shown that the mean HbA_1c was 9.2% in Indian patients and diabetes control was worse in those with longer duration of diabetes (9.9 ± 5.5 years).[3] This data indicates poor glycaemic control and clinical inertia to initiate the insulin therapy in Indian patients with diabetes.[3]

Poor control in both the type 1 and type 2 diabetes leads to multiple metabolic abnormalities, serious complications and reduced lifespan.[4-6] The UKPDS study[7] has highlighted the benefits of optimal glycaemic control and the risk reduction associated with it. For every 1% decrease in HbA_{1c}, the risk of any diabetes-related endpoint or diabetes-related death is decreased by 21%.[7] Therefore, tight regulation of HbA1c is critical in reducing the high disease burden of diabetes. However, tight control of HbA_{1c} runs the risk of increased hypoglycaemia. Therefore, diabetes management involves a delicate balance between the risk of hypoglycaemia while maintaining optimal glycaemic control.[8-9]

Insulin Therapy for Diabetes

Insulin is the mainstay of therapy in diabetes management. In type 1 diabetes, glycaemic control necessitates insulin treatment from the time of diagnosis.[10] In type 2 diabetes, most patients eventually require insulin therapy due to deteriorating glycaemic control and failure of Oral Anti-diabetic drugs (OADs).[11-12]

Insulin was discovered in 1921, and has since been used to treat diabetes.[13] Early formulations were fairly crude, impure animal preparations associated with many side effects. Immunogenicity, unpredictable availability and variability of animal-based formulations led to difficulty in determining proper doses and achieving

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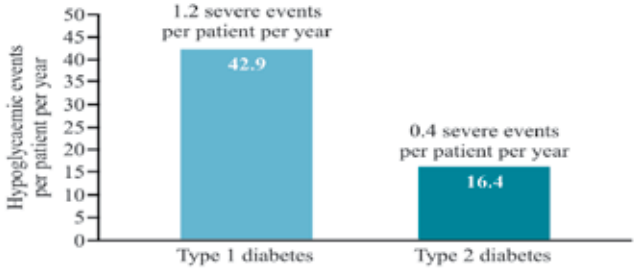

Fig. 1 : Hypoglycaemia in Diabetes[25]

good glycaemic control.[14-16] Development of refined human insulins has eliminated many of the earlier problems.[14-17]

Earlier human insulins consisted of preparations that were either short acting (e.g. regular insulin) or intermediate acting forms (Neutral Protamine Hagedorn, NPH). Later, synthetic insulin analogues, either short-acting (e.g. lispro, aspart) or long-acting (e.g. glargine, detemir) were developed. Synthetic long-acting (basal) insulin analogues were developed in order to provide a more physiological pharmacokinetic (PK) / pharmacodynamic (PD) profile compared with earlier insulins.[15] These synthetic analogues had some changes in the amino acid sequence compared to human insulin. Human insulin consists of an A-chain of 21 amino acids and a B-chain of 30 amino acids.[15] Changes in the insulin molecule have focused on the B-chain, thereby avoiding receptor-binding elements.[17] Insulin glargine (IGlar) has two molecular modifications on the B chain: elongation of the C-terminus of the B-chain plus two arginine residues inserted at position B30, and replacement of asparagine with glycine at position A21.[16] Insulin detemir (IDet) is modified by the deletion of the amino acid threonine at position B30 of the human insulin molecule and the addition of a 14-carbon myristoyl fatty acid acylated to lysine at B29.[18]

In type 1 diabetes, insulin is administered as a basal-bolus regimen; the basal dose provides long duration insulin coverage while the bolus dose is given prior to meals for short-duration insulin coverage.[19]

Insulin regimens in type 2 diabetes are more complex, as there oral anti-diabetic drugs (OADs) and/or insulins are used. The commonly used OADs include: metformin, sulphonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP-4I), glucagon-like peptide-1 (GLP-1) receptor agonists and alpha glucosidase inhibitors. In the stepwise approach for the management of type 2 Diabetes the first medication used is usually an OAD.[20] If glycaemic control is not achieved, complex regimens (two-drug and three-drug combinations), which may include basal insulins, are started. Long-acting basal (e.g. IGlar and IDet) or premixed insulin (e.g. biphasic insulin aspart) is generally the initial choice for insulin therapy, the dose depending on the degree of hyperglycaemia.[20-21] More complex insulin strategies are eventually required in type 2 diabetes; these include basal or basal-bolus regimens with or without OADs.[20]

In basal insulin therapy, long-acting basal insulin analogues (e.g. IGlar and IDet) are preferred over intermediate-acting NPH insulin because they do not have a pronounced peak effect, have more prolonged activity and have less day-to-day variability, resulting in both fewer symptoms and less nocturnal hypoglycaemia.[22] Additionally Insulin Detemir is also associated with less weight gain.[23] However, even with the use of the newer, long-acting basal insulins (IGlar, IDet), there remain many barriers to optimising insulin therapy to get the desired glycaemic control.

Barriers to Insulin Therapy

There are many barriers to Insulin therapy limiting its use in the diabetic patients.

Hypoglycaemia

The primary safety concern with any insulin therapy is hypoglycaemia.[8-9] It is a common, unpredictable and potentially dangerous side effect of pharmacotherapy for patients with diabetes. The American Diabetes Association (ADA) workgroup on hypoglycaemia defined hypoglycaemia as "any abnormally low plasma glucose concentration that exposes the subject to potential harm" with a proposed threshold of plasma glucose < 70 mg/dL (< 3.9 mmol/L) (ADA, 2005). The European Medicines Agency, on the other hand, recommend a lower threshold of plasma glucose (< 3.1 mmol/L or < 56 mg/dL) to define hypoglycaemia to allow for a more robust detection of clinically relevant hypoglycaemia with different treatment regimens.

Hypoglycemia is categorised as severe if the event requires the assistance of another person and as non-severe if it does not need any assistance.[24] Non-severe hypoglycaemic events (NSHEs) account for the majority of total events[25] as shown in Figure 1, but severe events carry great concern because they can be associated with cognitive impairment, behavioural disturbances, loss of consciousness, coma and even death.[26]

A survey of 1404 patients with diabetes found that hypoglycaemia results in significant loss of productivity.[27] This lost productivity was greater following nocturnal non-severe hypoglycaemic events (NSHE) compared with daytime NSHE[27] and has a greater negative impact on health-related quality of life (HRQoL), compared with daytime NSHE.[28]

About 43% of all severe hypoglycaemic episodes in type 1 diabetes in the Diabetes Control and Complications Trial were nocturnal.[8-9]

Additionally, hypoglycaemia may increase the risk of cardiovascular events. According to a retrospective database analysis of > 800,000 US patients with type 2 diabetes, patients identified as having hypoglycaemic events had 79% greater odds of experiencing an acute cardiovascular event.[29]

Fear of hypoglycaemia is a risk factor for decreased adherence, leading to suboptimal insulin dosing and inadequate glycaemic control.[30] Current basal insulins (IGlar and IDet) have lower rates of hypoglycaemia compared to earlier insulins like NPH.[31-36] However, newer insulin analogues with an even lower risk of hypoglycaemia can further decrease morbidity and mortality associated with hypoglycaemia. It can also help in avoiding poor glycaemic control as a result of poor adherence.

Flexibility in Dosing

Currently used basal insulin like IGlar has mean duration of action (19.4 hours) and it is comparable to Insulin detemir.[37] But the dosing guideline for Insulin glargine states '*Lantus should be administered subcutaneously once daily at any time but at the same time each day*'.[38] Thus, while the IGlar label does not imply the need for individual dosing frequency titration, it requires an inflexible dosing interval and advises to be given same time of the day which is not feasible practically. Altering the time of dosing (e.g., morning vs. evening) with both IDet[39] and IGlar[40] may affect the glycaemic profile, resulting in worsening morbidity.

Inflexible dosing intervals might impact the adherence to therapy. Proper adherence to regimen is essential and translates to better glycaemic control; in a type 2 diabetes study, each 25% improvement in adherence was associated with an HbA_{1c} decrease of 0.34%.[41] Regimens with fixed injection times have a risk of poor adherence. In the GAPP2™ survey conducted with a fixed regimen, 7.4% of patients admitted that they forget to take their insulin and 18.9% reported that their 'busy' lifestyles accounted for missed doses.[42] 27.6% of patients who missed insulin doses indicated they had difficulty taking their insulin at the prescribed time and 85.8% of physicians said they wished insulin treatments could be more flexible.[42]

Administering insulin at fixed times may not be convenient for the patients.[17] It may result in intentional omission. In another study, 'intentional' omission was reported by more than half (57%) of respondents in a sample of 502 adults with diabetes using insulin, with 20% regularly omitting necessary injections.[43]

Therefore, clinicians need to have options for regimens that are more flexible and less likely to fail due to poor adherence.[44]

Variability

Using insulin therapy to achieve the target levels of glycaemic control with avoiding hypoglycaemia is a challenging task. Variability in insulin action leading to difficulties with dose adjustment is an important confounding factor, which is often neglected. This glycaemic variability also reflects the variability in the glucose-lowering action of the insulin used in the therapy. The possibility for insulin-induced glucose variability is particularly high with basal insulins because of their prolonged absorption from high-dose depots. Pharmacodynamic (PD) variability manifests as both fluctuations in the level of glucose-lowering effect over time, and as inconsistencies in the response from one injection to another. The pharmacokinetic and pharmacodynamic studies have shown that many injected basal insulin products have high variable absorption with correspondingly variable action. Incomplete re-suspension and precipitation appear to be important issues with regard to unpredictability in this action, while an inadequate duration of action relative to the dosing interval results in a fluctuating action profile.

Heise *et al* have studied coefficient of variation (CV) to compare the within-subject variability in pharmacodynamic end points for insulin detemir, NPH insulin, and insulin glargine in subjects with type 1 diabetes and shown insulin detemir (CV = 27%) was associated with significantly less within-subject variability than both NPH insulin (CV = 68%) and insulin glargine (CV = 48%).[45]

The variability in insulin action is an important issue with existing basal insulins which further increases the risk of hypoglycaemia and decreases treatment adherence, often leading to poor glycaemic control.

Weight Gain with Insulin Therapy

Use of Insulin is often associated with undesirable weight gain. Currently available insulins barring insulin detemir are associated with weight gain as a major side effect limiting their use. Insulin detemir has shown less weight gain as compared to NPH Insulin.[46-47] and offers a better option as basal insulin.

New options to balance the need and barriers of Insulin therapy – Insulin Degludec

The pressing unmet need is for a newer insulin analogue with a longer duration of action (i.e.,

increased half-life), flexible dosing, flat peakless profile leading to less variability and a low rates of hypoglycaemia. A long duration of action would preclude the need for individual titration of dosing frequency. A once daily dose would be applicable to all individuals. Flexibility of dosing could significantly improve adherence. A low rate of hypoglycaemia will reduce morbidity related to both treatment and poor adherence.

As described in the following articles in this supplement, Insulin degludec is basal insulin with an ultra-long duration of action. It allows once daily administration for all subjects with the possibility of flexible administration whenever needed and low incidence of hypoglycaemia. These desirable characteristics could in turn, improve patient compliance and better treatment adherence leading to improvement in glycaemic control and decrease morbidity and mortality associated with diabetes.

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