Insulin Detemir – A novel long acting insulin analog

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ABSTRACT

Insulin detemir is a novel long-acting insulin analogue with a unique mechanism causing prolonged duration of action. This is because of its self-association into hexamers and dihexamers and to bind reversibly to albumin. Insulin detemir remains soluble after it is injected. Clinical studies showed insulin detemir administered once or twice daily is as effective as NPH insulin and insulin glargine in achieving glycaemic control. Most trials shown that insulin detemir exhibits less intra-patient variability in glycaemic control compared with NPH insulin and insulin glargine. One of the benefits of insulin detemir is its favorable effect on bodyweight. In addition, a reduced risk of nocturnal hypoglycaemia has been reported with insulin detemir compared with NPH insulin in patients with diabetes. These data indicate that insulin detemir is a valuable option for basal insulin therapy in patients with type 1 or type 2 diabetes.

Key words: Insulin detemir, variability, weight gain, hypoglycemia, glycaemic control.

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetic and environmental factors [1]. It is well known that the prevalence of type 2 diabetes mellitus (DM) is rising globally having a marked impact in developing countries like India. South East Asians especially Indians have a racial predisposition and other unique risk factors to develop DM to a greater extent. In India there is increasing urbanization and industrialization which has led to physical inactivity, sedentary lifestyle, psychosocial stress and obesity leading to progressive increase in prevalence of DM [2].

The World Health Organization (WHO) [3] has projected that the global prevalence of type 2 DM will increase from 135 million in 1995 to 300 million by the year 2025. The greatest increase will be in India from 19.4 million to 57.2 million.
The current studies in India indicate that there is an alarming rise in prevalence of diabetes which has gone beyond epidemic form to a pandemic[4,5].

**Goal of treatment**

Insulin is the primary treatment for all patients with type 1 DM, for patients with type 2 DM who are not controlled adequately by diet and/or oral hypoglycemic agents, as well as for patients with post-pancreatectomy diabetes or gestational diabetes. In addition, insulin is critical for the management of diabetic ketoacidosis, hyperglycemic, non-ketotic coma and in the perioperative glycaemic management of both type 1 and 2 DM.

The aim of diabetic treatment is to bring the blood glucose as near to normal as possible. Optimal treatment requires a coordinated approach to diet, exercise, oral hypoglycemic agents and the administration of insulin [6].

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous insulin is secreted into the portal venous system. Thus, exogenous insulin administration exposes the liver to sub-physiologic insulin levels. No insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet [1].

**Common multidose insulin regimens[6]**

1. Typical split-mixed regimen
   a. consisting of twice-daily injections of a mixture of regular(regular/lispro/aspart) and intermediate-acting (NPH or lente insulin).
   b. a variation is done in which the evening dose of intermediate-acting insulin is delayed until bedtime to increase the amount of insulin available the next morning.
   c. a regimen that incorporates only ultra-lente or glargine insulin.
   d. a variation that includes pre-meal short-acting insulin with intermediate-acting insulin at breakfast and bedtime

2. Insulin administration with a regimen of continuous subcutaneous insulin Infusion.

Any type of diabetes if well controlled by using OHA/insulin prevents long term microvascular and macrovascular complications. But while we stringently control the blood sugar there is possibility of complications like hypoglycemia may occur [6]. This hypoglycemia may be dangerous in children and elderly patients and if the blood sugar is fluctuating then the long term complications of diabetes like blindness, renal failure, coronary artery disease, stroke, diabetic ulcer and many more complications are difficult to prevent. Any insulin by its nature is mitogenic can cause weight gain which again complicates the whole scenario [11].

The present day analogue insulins address most of these issues associated with conventional insulins. Insulin detemir has an edge over the other existing insulin preparations. i.e. it is weight neutral as well [10].
Structure:

Salient features:
Insulin detemir is a long-acting insulin analogue produced by recombinant DNA technology with expression in *Saccharomyces cerevisiae* followed by chemical modification [12].

- Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been removed and a 14-carbon, myristoyl fatty acid has been acylated to lysine at B29 [13,14].
- Des-threonine myristic (mir) acid is the non-proprietary name for De-te-mir.
- The mechanism behind the longed action of insulin detemir is primarily considered to be due to:
  1. self-association to hexamers upon injection;
  2. tendency to form hexamer – dihexamer complexes; and
  3. reversible albumin binding in the circulation after absorption [15].

- The addition of the fatty acid also allows insulin detemir to be formulated as a solute in a neutral liquid solution, which does not precipitate during administration or absorption.
- Mechanism of protraction of detemir may contribute to the reduced variability in insulin action observed with its use [16].

Tissue albumin bound insulin detemir along with its dihexameric forms may act as a buffer and fatty acid stabilizes it against changes in insulin absorption rates, thus reducing the risk of hypoglycaemia. This stable, soluble profile of insulin detemir contrasts with that of NPH insulin, which is delivered in a preformed crystalline/precipitate suspension, and with that of insulin glargine, which precipitates from its acidic solution in the neutral subcutaneous tissue after injection. The precipitation and dissolution of a precipitate are unpredictable processes [10].

In *vivo* animal studies have confirmed that the prolonged effect of insulin detemir results from the slow absorption of insulin molecules, as well as its reversible binding to albumin [10].

C57Bl/6 mice were injected i.v. with either insulin detemir or human insulin and Western blot analysis was performed on liver, muscle, hypothalamic and cerebrocortical tissues. Moreover, cerebrocortical activity was detected by EEG in awake mice and cerebral insulin concentrations were measured following human insulin and insulin detemir injection.

The time course and extent of IR (insulin receptor) phosphorylation in peripheral tissues were similar following insulin detemir treatment compared with human insulin, but insulin signalling in hypothalamic and cerebrocortical tissue determined by tyrosine-phosphorylation of the IR and Irs2 proteins occurred faster and was enhanced due to a higher insulin detemir concentration in the brain [17].
Pharmacology:
In a clinical trial [9] participants were randomly allocated to SC injections of 0.4, 0.8 and 1.4 U/kg of either insulin detemir (24 nmol/U) or insulin glargine (6 nmol/U) on three occasions. On the remaining three occasions, all the participants were treated with 0.8, 1.6 and 2.8 dosing unit (DU)/kg of NN344 (6 nmol/DU).

Following dosing, the blood glucose (BG) concentrations were kept constant at the target level by variable intravenous infusion of glucose administered by the Biostator, which automatically calculated the appropriate adjustments of an intravenous glucose infusion rates (GIR). Duration of action was defined as the time from trial drug administration until smoothed GIR profile was consistently below 0.5 mg/kg/min. In addition, the effects of the study medication on the suppression of free fatty acids (FFA) and endogenous glucose production (EGP) were described by calculating the area over the curve (AOC) (smoothed) from 0–24 h. Thus, from these data, it seems that both insulin glargine and insulin detemir, and potentially also NN344, are suited for once-daily administration in the majority of individuals with type 2 diabetes. Previous data from healthy people and from individuals with type 1 diabetes indicated a duration of action close to 24 h with insulin glargine even in doses as low as 0.3 U/kg, whereas the metabolic effect of insulin detemir lasted for about 20 hr [3,8,17].

When administered as a single dose ranging from 0.2 to 1.6 U/kg, insulin detemir has shown dose-proportional effects in plasma AUC over 24 hours and maximum concentrations of plasma insulin detemir in patients with type 2 diabetes. In healthy volunteers, insulin detemir has been shown have a more predictable pharmacokinetic profile than NPH insulin. More recent studies have confirmed that intrapatient variability in pharmacokinetic endpoints is lower with insulin detemir than with NPH insulin or insulin glargine in patients with type 1 and type 2 diabetes [8-10, 18].

Twenty-seven insulin-treated men with type 2 diabetes were enrolled in this randomized, double-blind trial and participated in six euglycaemic glucose clamp experiments. Participants received NN344 in three experiments at a dose of 0.8, 1.6 and 2.8 dosing units (DU) per kilogram of body weight. In the other three experiments, the participants received 0.4, 0.8 and 1.4 U/kg of either insulin detemir or insulin glargine. In individuals with type 2 diabetes, the time-action profiles and the duration of action of the albumin bound insulin analogues, insulin detemir and NN344, were comparable with those of insulin glargine, whereas within subject variability in the metabolic effect was significantly lower. Therefore, insulin detemir and NN344 seem to be as well suited as insulin glargine for once-daily administration in type 2 diabetes [8,9]. Insulin detemir is licensed for once- or twice daily administration and, in contrast to glargine, has been studied most frequently with a twice-daily injection schedule.

Metabolism:
The data suggest that insulin detemir can be used in children and adolescents with type 1 diabetes using titration guidelines similar to those used in adults. Moreover, insulin detemir may offer the advantage of greater predictability of response in comparison to NPH insulin due to lower total variability and a lesser degree of kinetic disparity across age-groups [19]. Results suggest that neither renal nor hepatic impairment exert a clinically important influence on the PK of insulin detemir although the number of subjects was small [20] and there are no differences in patients of different race or ethnicity [16].
Pharmacodynamics:[10]

- *In vitro* studies have suggested that insulin detemir functions as a full agonist of insulin receptors. However it has a lower affinity than human insulin for human insulin receptors.
- Binding to the insulin-like growth factor-1 receptor, which is associated with increased *in vitro* mitogenicity, is significantly less with insulin detemir than with human insulin and insulin glargine.

Moreover, a recent *in vivo* study of how insulin detemir activates the insulin receptor-signalling cascade demonstrates that insulin detemir preferentially acts in the brain, despite unaltered insulin receptor signalling in the peripheral tissues [17].
- In addition, insulin detemir may be associated with a relative reduction in lipogenesis. The preferential insulin signalling activity in the brain associated with insulin detemir has been theorized to have appetite-suppressive effects, may benefit individuals with diabetes who are overweight and offers a potential explanation for some of the reduced weight gain observed with insulin detemir.

Comparative clinical trial:
Type I - Diabetes mellitus:
- This meta-analysis included 4 multinational, open-label, randomised phase III trials in people with Type 1 diabetes, treated with a basal bolus regimen with insulin detemir (n=1336) or NPH insulin (n=814) in combination with pre-meal regular insulin or insulin aspart for 16 weeks up to 6 months. Comparison of hypoglycaemia incidences demonstrated an estimated reduction by 5.26 episodes per person per year for insulin detemir relative to NPH insulin. Mean coefficient of variation (CV) for the within-person variation in self measured fasting blood glucose was lower with insulin detemir than with NPH insulin across trials [21].
- In this 26-week, multicentre, open-label, parallel-group trial, 320 subjects with Type 1 diabetes received either insulin detemir twice daily or insulin glargine once daily each in combination with pre-meal insulin aspart. After 26 weeks, HbA1c had decreased from 8.8 to 8.2% in the insulin detemir group and from 8.7 to 8.2% in the insulin glargine group. Home measured fasting plasma glucose (PG) was lower with insulin glargine than with insulin detemir (7.0 vs. 7.7 mmol/l, *P* <0.001). Overall, there was no significant difference in within-subject variation in PG (*P* =0.437). Within-subject variation in pre-dinner PG was lower with insulin detemir than with insulin glargine (*P* < 0.05). The risk of severe and nocturnal hypoglycaemia was 72% and 32%, respectively, lower with insulin detemir than with insulin glargine (*P* < 0.05) [22]. Similar study open-label, randomized (2 : 1), parallel-group study, 347 (140 prepubertal and 207 pubertal) children with Type 1 diabetes, aged 6–17 years, received insulin detemir (n= 232) or NPH insulin (n= 115) once or twice daily, according to the pre-study regimen, plus pre-meal insulin aspart showed similar results [23].

This was a 6-month, prospective, randomized, open-label, controlled, parallel-group trial conducted on 749 pts at 92 sites in Europe and Australia. After 6 months, FPG was lower with insulin detemir than with NPH (–1.16 mmol/L difference; *P* = 0.001), whereas HbA1c did not differ significantly between treatments (–0.12% [95% CI, –0.25 to 0.02]; *P* = NS). There was a 26% reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH (*P* = 0.003). Gain in body weight was significantly lower after 6 months with insulin detemir than with NPH (–0.54 kg difference; *P* = 0.024) [4,5].
- A published and validated computer simulation model was used to project long term economic and clinical outcomes in a simulated cohort of type 1 diabetes patients treated with insulin detemir plus insulin aspart or Neutral Protamine Hagedorn plus human soluble insulin in a UK setting. Quality-adjusted life expectancy (QALE) was 0.66 quality-adjusted life years (QALY) higher in the analogue insulin versus the human insulin group (mean ± SD) (7.65 ± 0.09 versus 6.99 ± 0.08). Direct lifetime costs were £1654 greater with analogue versus human insulin.
treatment (£40 876 ± 1119 versus £39 222 ± 1141), producing an incremental cost effectiveness ratio (ICER) of £2500 per QALY gained [24].

**Type II- Diabetes mellitus**

- This was a 26-week, multinational, open-label, parallel group trial with 505 patients with type 2 diabetes treated for 26 weeks with insulin detemir plus insulin aspart at mealtimes, experienced comparable glycaemic control but significantly lower within-subject variability and less weight gain compared to patients treated with NPH insulin and insulin aspart. Insulin detemir was well tolerated and had a similar safety profile to NPH insulin [25,26].
- Data were pooled from two randomized, parallel group trials of 22 and 24 weeks duration, in which 900 insulin-treated patients with type 2 diabetes mellitus had their treatment intensified to basal-bolus therapy. Patients received once- or twice-daily insulin detemir or neutral protamine Hagedorn (NPH) insulin in conjunction with insulin aspart or human soluble insulin at mealtimes. Patients treated with insulin detemir had minimal weight gain (mean <1kg), regardless of their BMI at entry (estimated slope −0.032), whereas, in patients treated with NPH insulin, weight gain increased as baseline BMI increased (estimated slope 0.075, p = 0.025) [27].
- In the 9 phase III studies of basal-bolus therapy where weight change data are available, the advantage for Insulin Detemir is very clear and consistent, reaching statistical significance in every case.

Standl and De Leeuw did 1-year studies, where it is interesting to note that the weight gain with NPH insulin was in excess of 1 kg, with no weight gain with insulin detemir [10].
• Patients with type 2 diabetes who were transferred to insulin detemir + oral antidiabetic drugs (OADs) from an OAD-only regimen (n = 1321), NPH insulin+ OADs (n = 251) or insulin glargine + OADs (n = 260) for 3 months. Among all groups, 3 months after starting treatment with insulin detemir, total, daytime and nocturnal hypoglycaemic events/patient were reduced by 84, 80 and 90%, respectively, from baseline. HbA1c was significantly reduced from baseline in each of the subgroups (1.29, 0.60 and 0.59% for patients previously taking OADs only, NPH insulin OADs and insulin glargine OADs respectively; (p < 0.0001), as was fasting blood glucose (FBG) (58.1, 29.1 and 24.6 mg/dl; p < 0.0001) and FBG variability (8.2 mg/dl, 5.7 mg/dl; p < 0.0001 and 5.1 mg/dl; p < 0.0008) [28].

• Data from a 24 weeks insulin add-on to current OAD therapy study in insulin naïve people with type 2 diabetes (n=475) were analyzed. Mean HbA1c decreased by 1.84% and 1.90% points with detemir and NPH insulin, respectively, to endpoint values of 6.58% and 6.46% (NS). Regardless of baseline BMI, people with type 2 diabetes gained less weight with detemir than with NPH insulin [29].

• Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation is a large, multi-national, open-label, prospective, observational study assessing the safety and efficacy of insulin detemir in clinical practice. A total of 20,531 patients with type 1 or 2 diabetes from 11 countries were prescribed insulin detemir and followed up after a mean of 14.4 weeks. The 14-week observations from PREDICTIVE support clinical trial data showing that insulin detemir improves glycaemic control, with a lowered risk of hypoglycaemia and no weight gain [30].

• This was a 22-week, multinational, open-labeled, symmetrically randomized, parallel group trial including 395 people with type 2 diabetes (IDet+ IAsp: 195, NPH+ HSI: 200). Basal-bolus treatment with IDet + IAsp is an effective and well tolerated insulin regimen in people with type 2 diabetes, resulting in glycaemic control comparable to that of NPH + HSI, but with the advantages of less weight gain and a lower day-to-day within-person variation in FPG [27].

PREDICTIVE 303 was a 26 week, prospective, randomized, open-label, multi-center study in patients with type 2 diabetes that investigated whether patient-driven adjustments of insulin detemir doses using the 303 Algorithm achieved similar glycaemic control compared to standard-of-care, physician-driven adjustments in doses. Reductions in HbA1c from baseline were similar between those patients in the 303 Algorithm and Standard-of-care groups (−1.1 and −1.0%, respectively; between group p = 0.0933); patients in the 303 Algorithm group achieved a greater reduction in FPG [31].

Insulin detemir is associated with no weight gain in type 1 diabetes and with less weight gain than NPH insulin in type 2 diabetes. A post-hoc analysis of data from a study of 475 insulin-naïve type 2 diabetes patients analyzing weight change in relation to baseline BMI showed that the reduced weight gain was dependent on body mass index (BMI) at initiation of treatment. Patients were administered insulin detemir or NPH insulin twice-daily (morning and evening) as add-on to existing treatment with oral blood glucose lowering agents. Glycaemic control was similar between treatments. When compared to NPH insulin, patients who received Detemir gained less weight regardless of baseline BMI. The interesting fact was that with increasing baseline BMI, patients gained less weight with insulin detemir; a relationship which was not found with NPH insulin [7].

Adverse reactions:
• Gastro-intestinal disorders (pain, nausea and vomiting) were most common in patients receiving insulin detemir (1.5% of patients) [25].
• Administration site conditions (0.03%), dermatitis, oedema, pain and injection site reaction [26-30].
• Hypoglycaemia (0.16%) [30].
• Insulin detemir has been shown to reduce the risk of hypoglycemic episodes in number and in severity compared with NPH [32,33].
• It is most important that significantly less weight gain and even weight loss has been observed in clinical trials with insulin detemir [32].

Drug interactions:
Despite this high level of albumin binding, insulin detemir is not likely to be involved in competitive drug interactions at the albumin binding site as there is a vast excess of albumin-binding sites available to each drug molecule [16]. In these studies, no interactions have been reported between insulin detemir and a series of free fatty acids or drugs such as phenylbutazone, warfarin, ibuprofen, diazepam, tolbutamide, glibenclamide, aspirin or valproate [10].

Dosage and administration:[16].
The dosage of insulin detemir should be individualized according to the patient’s needs, with the following suggestions:
- For insulin-naïve patients who are not achieving glycaemic goals on OADs - Start with either 0.1 or 0.2 units/kg or 10 units once daily at the evening mealtime or bed time and titrate gradually (upward or downward) to achieve desired glycaemic goals.
- For patients who require twice-daily insulin dosing for effective control, the evening dose can be administered with the evening meal, at bedtime, or 12 h after the morning dose.

Patients already treated with basal insulin can transit to insulin detemir on a unit-to-unit basis. It has to be administered subcutaneously either in thigh, abdominal wall, or upper arm.
Because of pH differences that could affect the action profile and efficacy of each, insulin detemir should not be mixed with other insulins. It is available as 3 mL prefilled FlexPen (100 units/mL) 10 mL vials which when unopened can be stored at room temperature for 42 days or in the refrigerator until the expiration date without loss of potency.

Brand
The newer long-acting insulin analog, insulin detemir, is an excellent option for patients with diabetes who need a basal insulin replacement that closely mimics a peak less physiological basal insulin release. In comparative trials with other basal insulin preparations, insulin detemir has been shown to improve glycaemic control with decreased within-patient variability, decreased incidence of hypoglycemia, including nocturnal hypoglycemia, and less weight gain. Given that the most difficult part of initiating insulin therapy often is overcoming patient and provider fears leading to clinical inertia, the availability of insulin detemir may help alleviate some of this difficulty and improve outcomes for patients with diabetes.

CONCLUSION
Insulin detemir is at least as effective as NPH insulin and insulin glargine in maintaining glycaemic control in patients with type 1 and type 2 diabetes. Because insulin detemir provides prolonged and consistent glycaemic effect of up to 24 hours, it can be administered once daily. Insulin detemir is clearly associated with less variable insulin action compared with NPH insulin and, in some studies, insulin glargine. In addition, insulin detemir exhibits weight neutrality/less weight gain in patients with type 1 diabetes and type II diabetes.
Most trials have also demonstrated that insulin detemir is associated with a reduced risk of hypoglycemia compared with NPH insulin. A reduced risk of nocturnal hypoglycaemia has also been reported with insulin detemir compared with insulin glargine of the equivalent efficacy, with reduced within-patient variability, and better weight profile of insulin detemir. Its’ use may help patients and providers to optimize diabetes management and achieve glycaemic goals [10,34-37]. Insulin detemir may offer a weight advantage over NPH insulin, especially in overweight or obese people with type 2 diabetes initiating insulin therapy.

Longer acting insulins were superior mostly in their nocturnal effect, which resulted in a lower level of fasting glucose levels and fewer episodes of nocturnal hypoglycaemia. No data on long term complications were available. Analysis of the currently available long-term trials comparing long acting insulin analogues with NPH insulin showed that insulin glargine and insulin detemir were almost identically effective compared to NPH insulin in long-term metabolic control (HbA1c). The currently available data can not substantiate conclusions on the benefits and risks of long acting insulins, and long-term data are of need. Until long-term data on benefit and risk are available, we suggest a cautious approach to treatment with insulin glargine or insulin detemir [38,39].

Currently there are 112 trial ongoing, out of which 50 are already completed and 34 are currently recruiting patients for insulin detemir trials [40].

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REFERENCES
[12] Patient Information Sheet Insulin detemir [rDNA origin] injection (marketed as Levemir) Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570