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Insulin detemir: a new basal insulin analogue

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Basal insulin therapy is an integral part of the intensive management of type 1 diabetes and it is also often used in type 2 diabetes. An ideal insulin regimen in patients with diabetes would mirror the 24-h insulin profile of a non-diabetic person, thereby preventing hyperglycaemia without inducing hypoglycaemia. Until recently, available insulins have pharmacokinetic disadvantages, compared to physiological insulin secretion. Insulin detemir is a new basal insulin analogue recently available for commercial use in the UK. Clinical trials have demonstrated lower fasting plasma glucose levels, lower variability in plasma glucose, predictable action profile and a reduced risk of nocturnal hypoglycaemia and weight gain, compared to conventional basal insulins. This study reviews the properties and potential use of insulin detemir.

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Introduction

Currently, the therapeutic challenges in the treatment of both type 1 and 2 diabetes mellitus (DM) are the maintenance of near normal glycaemia in order to prevent long-term complications [1,2] and the avoidance of episodes of hypoglycaemia. For many people with DM, intensive insulin therapy means multiple insulin injections and frequent blood sampling at the expense of an increased risk of hypoglycaemia.

Normal insulin secretion consists of two discrete components: low basal levels secreted between meals, through the night and during fasting, and very high levels secreted postprandially. Basal–bolus insulin regimens attempt to reproduce this insulin secretion profile, which consists of one or two injections per day of intermediate or long-acting insulins (basal) and multiple mealtime (bolus) injections of rapid acting or regular insulins. Ideal basal insulin should have a 24-h peakless activity allowing once-daily dosage.

The disadvantages of conventional insulin preparations include variable absorption with considerable intra- and interpatient variation, pronounced peaks after injections and prolonged duration of action all contributing to the difficulty in obtaining normoglycaemia (table 1). Hypoglycaemia is often the limiting factor in the maintenance of tight glycaemic control [3]. Hypoglycaemia ranks high among the fears of patients using insulin and results in a decrease in the quality of life and a reduced awareness of subsequent hypoglycaemia, thereby an increased risk of severe hypoglycaemia [4,5].

Conventional Basal Insulins

Conventional intermediate- and long-acting insulins have an onset of action of 0.5–4 h, a maximal effect at 4–20 h and a duration of 8–36 h (table 1). The absorption pattern of conventional long- and intermediate-acting insulins puts many patients at the risk of nocturnal

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Table 1 Pharmacokinetics of current insulin preparations

Type of insulin	Onset	Peak effect	Duration (hours)
Rapid acting			
Insulin lispro (Humalog)	0–15 min	30–90 min	<5
Insulin Aspart (Novorapid)	0–15 min	30–90 min	<5
Short acting			
Regular human Insulin (Humalin S and Actrapid)	30–45 min	2–4 h	6–8
Intermediate acting			
Semilente	0.5–1 h	4–6 h	8–12
Lente	2–4 h	6–10 h	12–24
Isophane	2–4 h	6–10 h	12–24
Long acting			
Ultralente	3–4 h	8–20 h	20–36
Protamine zinc	3–4 h	14–20 h	24–36
Long acting anlogues			
Glargine	2 h	Lacks pronounced peak	22
Detemir	2 h	Lacks pronounced peak	20 for doses of >0.4 U/kg

hypoglycaemia, even despite avoidance measures, such as a bedtime snack or taking the basal insulin later at bedtime. Because the effect of the evening dose of insulin wanes towards the morning, some patients may develop hyperglycaemia. Even the longest-acting human insulin preparation – ultralente – produces peak insulin level at 12–16 h and often does not provide adequate basal insulin supplementation when injected once daily. These factors contribute to the instability of blood glucose with fluctuations from hypoglycaemia especially at night and to hyperglycaemia particularly in the fasting state. Nocturnal hypoglycaemia occurs in up to 40% of patients with type 1 DM [6] and can lead to a failure to achieve good glycaemic control. Thus, the clinical challenge is to find an insulin sufficient to control the fasting blood glucose without causing nocturnal hypoglycaemia.

Insulin Detemir

Insulin detmir is a basal insulin analogue designed to bind reversibly to albumin following injection and absorption [7,8]. Insulin detemir is soluble at neutral PH and its molecular structure differs from that of human insulin by the omission of threonine at position B30 and the attachment of myristic acid, a C14 fatty acid chain, to lysine at position B29 [9] (figure 1). Myristic acid contributes to the aggregation of insulin detemir hexamers, delays subsequent dissociation and absorption and facilitates >98% binding of insulin detemir to albumin molecule in plasma and interstitial fluid [8].

Following injection, insulin detemir forms a liquid depot in the subcutaneous tissue and resembles as hexamers and then binds to tissue-bound and free interstitial albumin. Albumin molecule may carry hexamers, diamers and monomers of insulin detemir. Only free dissociated insulin detemir can penetrate capillary walls; free hexamers and diamers penetrate capillary wall more slowly than monomers. While the majority of protraction of action of insulin detemir results from its lengthy absorption from the subcutaneous depot, its action is additionally prolonged following absorption through reversible binding to albumin in the plasma [10].

Duration of Action and Variability

Insulin detemir was showed to have a dose-dependent duration of action [11]. With the dose of 0.4 U/kg, the duration of action is approximately 20 h, therefore suggesting the feasibility of once daily dose [11], for doses of <0.4 U/kg administration twice daily is advisable to cover 24 h. However, detemir's predictability allows the clinicians to determine very quickly whether it is needed once or twice daily.

Insulin detemir is likely to be less susceptible to variability in action than other basal insulins. Being soluble, resuspension is not required and it does not form a precipitant upon injection; these will remove two potential causes for variation [10]. It is also likely that plasma albumin binding could buffer the effect of short-duration changes in the depot absorption rate, thereby limiting pharmacodynamic variability. A study reported that,

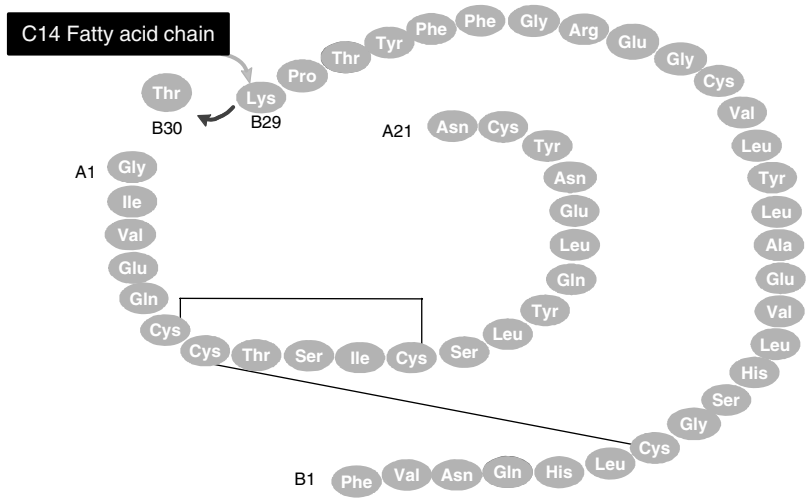

Fig. 1 Molecular structure of insulin detemir showing the deletion of threonine from the position B30 and acylation of the C14 fatty acid chain (myristic acid) at position 29 on the β-chain.

among 54 persons with type 1 DM, within-participant variability for glucose infusion rate time curve was significantly less with insulin detemir, compared with NPH and insulin glargine [12]. Similar findings were observed in people with type 2 diabetes [13].

No significant differences in the pharmacokinetic properties of insulin detemir was observed in children and adolescents, compared with adults with type 1 DM [14]. Further studies showed no relevant difference in pharmacokinetic of insulin detemir between healthy Caucasian and Japanese American people [15,16] or between people with renal or hepatic impairment and healthy people [17].

Clinical Efficacy

Several recent clinical trials have confirmed the more predictable action of insulin detemir relative to NPH insulin, and have also reported clinical benefits associated with its use.

A 6-month multinational parallel group comparison trial included 448 patients with type 1 diabetes, randomized to receive insulin detemir or NPH with the rapid-acting insulin aspart at meal times [18]. While glycaemic control was similar between both treatment groups, within-participant variability in self-measured FBG was lower in insulin detemir than in NPH insulin ($p < 0.001$). This was also associated with a significant reduction in the risk of hypoglycaemia and nocturnal hypoglycaemia (22 and 34%, respectively); this risk reduction is sustained over the course of the study. Nightly plasma glucose profiles were smoother and more stable with insulin detemir, compared to NPH insulin. In addition, body weight was significantly lower with insulin detemir at the end of the clinical trial.

In two other clinical studies of insulin detemir in type 1 diabetes, fasting plasma glucose was significantly lower compared to, NPH insulin [19,20]. A randomized, 6-month, open-label, parallel clinical trial, largely performed in the UK, compared once-daily insulin detemir or NPH insulin in combination with human soluble insulin in 747 patients with type 1 diabetes [19]. Analysis of self-monitored FBG readings showed significantly less variability during treatment with insulin detemir than with NPH insulin. The study, in addition, demonstrated significantly lower FBG at end point with insulin detemir than with NPH insulin. The risk of nocturnal hypoglycaemia was 26% lower in patients receiving insulin detemir. Furthermore, patients treated with detemir did not gain any weight, whereas those treated with NPH showed a mean weight gain of 0.4 kg. Another open-label, randomized, parallel, multicentre study compared the administration of insulin detemir at 12-h intervals and morning and bedtime with NPH morning and bedtime over 16-week treatment period in 408 patients with type 1 diabetes who used bolus insulin aspart at mealtimes [20]. At the end of the trial for each insulin detemir regimen, regardless of the time of administration, fasting plasma glucose was significantly lower, compared to NPH group. Within-participant variability in self-monitored FBG was lower in detemir groups; weight gain was lower in both detemir groups; the risk of nocturnal hypoglycaemia was 33% lower in the detemir morning and bedtime than the NPH insulin group but similar in the 12 hourly detemir and NPH group. In another study, insulin detemir treatment was associated with a favourable weight difference and reduced the risk of nocturnal hypoglycaemia, but the overall risk of hypoglycaemia and glycaemic control as measured by HbA1c, FBG and 9-point blood glucose

profile were comparable [21]. Finding of reduced variability in glycaemic parameters associated with a reduced risk of nocturnal hypoglycaemia and lack of weight gain have also been reported by other comparative studies in type 1 diabetes [22–24].

In people with type 2 diabetes, similar glycaemic control and hypoglycaemic risk were found with insulin detemir and NPH when used in combination with insulin aspart in a 6-month trial that included 505 patients [13]. However, treatment with insulin detemir resulted in less weight gain, compared with NPH insulin, more predictable and lower within-participant variability in fasting blood glucose [13].

Tolerability, Adverse Effects and Safety

Insulin detemir has been showed to be well tolerated with an overall adverse effect profile similar to NPH [21]. Serious adverse events occurred in 5.6 and 7.1% of patients in the insulin detemir and NPH group, respectively, in an open-label study of 308 patients with type 1 diabetes over 12 months [21]. In another open-label study of 36 patients, two patients discontinued insulin detemir because of adverse effects [16]. The most frequent adverse events were headache, dizziness and injection site reactions.

Furthermore, *in vitro* tests in human cell lines investigating binding to insulin and IGF-1 receptor sites have showed that insulin detemir has reduced receptor affinities for both receptors and hence a reduced effect on cell growth and mitogenicity, compared to human insulin [25]. The reduced *in vitro* potency of insulin detemir might explain why this analogue is not as effective, on molar basis, as human insulin in humans.

Recent Studies

More recent studies presented as abstract form in American Diabetes Association (ADA) and European Association for the Study of Diabetes annual meetings in 2004 have provided further data on the potential of insulin detemir. Three studies in patients with type 1 diabetes presented in ADA 2004 have demonstrated a lower risk of nocturnal [26] and overall hypoglycaemia [27], lower and more predictable FBG [26]. Body mass index was lower in detemir group at the end of one study [26]. Less within-participant variability, compared with NPH insulin has also been reported in both type 1 [28] and type 2 diabetes [29]. Treatment with insulin detemir, compared with NPH insulin, as add-on to oral hypoglycaemic agents resulted in a significantly less within-participant variation in pre-breakfast and pre-dinner plasma glucose, a lower risk of hypoglycaemia and less weight gain [30]. More than 70% in both groups achieved HbA1C level of $<7\%$. However, a significantly higher proportion of patients in insulin detemir group reached HbA1C of $<7\%$ in the absence of hypoglycaemia. There were no significant differences in glycaemic control as measured by FBG and HbA1C between the two groups.

A meta-analysis of four open-label, randomized, phase III trials in people with type 1 diabetes concluded that reduction in within-participant variability of FBS is a major contributor to reduced risk of hypoglycaemia with insulin detemir relative to NPH [31].

Conclusions

The availability of new basal insulin detemir offers several advantages over the use of NPH insulin, including lower risk of nocturnal and 24-h hypoglycaemia, lower and more predictable FBG, less weight gain and less within-participant variability. Disappointingly, there is no solid evidence to suggest better glycaemic control, compared with NPH insulin. Further studies to clarify this point and to assess cost-effectiveness, quality-of-life effect of insulin detemir and comparison between insulin detemir and glargine are needed.

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