Turkish Journal of Endocrinology and Metabolism, (2004) 1 : 1-7 **REVIEW**

Basal Insulin Analogues

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Introduction

In non-diabetic individuals, ingestion of food results in a rise of serum insulin concentration to a maximum after 30-45 min, followed by a decline to basal levels after 2-3 h. The currently available preparations of human insulin make it impossible to achieve sustained normoglycaemia. The onset of action of sc injected regular insulin is too slow, and the duration of its action is too long to mimic the insulin secretion pattern of healthy individuals during carbohydrate containing meal. Similarly, the available intermediate or long acting insulin preparations are unable to provide a stable, continous basal insulin level.

The goal of treatment of type 1 and type 2 diabetes is maintenance of long-term near-normoglycaemia to prevent the onset and / or progression of long-term complications. Therefore, to achieve tight glycaemic control, the need for new insulin preparations with a faster onset and shorter duration of action and long acting preparations with more flat time action profile became apperent.

Short-acting human insulin analogues lispro and aspart, which are absorbed faster than regular insulin improve 1- and 2-h postprandial blood glucose levels. However, beter postprandial blood glucose control with short acting insulin analogues results in improvment in glycaemic control in the long-term only by the extent to which replacement of basal insulin is optimized at the same time. A major barrier to achieving tight glycaemic contro is hypoglycaemia particularly nocturnal episodes. New long acting human insulin analogues with action profiles designed, to overcome these problems.

This review focuses on the use of new long-acting, basal insulin analogues in patients type 1 and type 2 diabetes.

Insulin Glargine

Insulin glargine is the first clinically available long-acting recombinant human insulin analogue made by modifiying human insulin using recombinant DNA technology. It differs from native human insulin in both the A and B subunits of the protein; the A- chain contains an asparagine to glycine substution at position 21, and the B-chain is elongated at the C-terminus by the addition of two arginene residues (1). The modification to the B-chain of the molecule shift the isoelectric point of the molecule towards neutral, while the A- chain modification conferns stability. These changes enable insulin glargine to remain soluble in the acidic environment of the vial, but form amorphous microprecipitates in the neutral pH of subcutanes tissue after injection (2). Results of pharmacodynamic activity characterised by a slower onset but longer duration of activity than NPH insulin. Insulin glargine has no peak effect and has almost constant glucose-lowering activity lasting 24 hours The rate of absorption of insulin glargine appers to provide a basal insulin level that remains constant for at least 24 hours. Importantly, absorbtion of the drug was similar irrespective of the site (arm, leg or abdomen) of administration. No accumulation of insulin glargine occured with daily sc injections in patients with type 1 diabetes (3). Insulin glargine is partially de graded in the subcutaneous

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tissue to two active metabolites M1 and M2. Both unchanged drug and metabolites are present in the plasma (4).

Insulin receptor binding kinetics of insulin glargine are similar to those of regular insulin. Mitogenic effects of insulin to be primarly mediated via the insulin-like growth factor-1 (IGF-1) and insulin glargine appers to have a higher affinity for the IGF-1 receptor than regular human insulin. However, in most cell types tested *in vitro*, mitogenic activity was similar between insulin glargine and regular insulin (5,6).

Physiological and biochemical responses to hypoglycaemia induced by insulin glargine in patients type 1 diabetes mellitus and healty volunteers were similar to those induced by regular insulin. In addition to the reduced inter-patient variability, reduced intra-patient variability has been demonstrated with insulin glargine in type 1 diabetes (6).

Once-daily subcutaneus injections of insulin glargine provide basal insulin levels for the treatment of adults or childreen (aged<6 years) with type 1 and adults with type 2 diabetes. In clinical trials, insulin-naive patients were started with a dose of 10 IU once daily and maintained at dosages ranging from 2-100 IU once daily. In patients receiving once-daily NPH, the initial dose of in sulin glargine was reduced by approximately 20% for the first week and then adj usted according to fasting blood glucose levels (1).

The incidence of adverse events with insulin glargine has been generally similar to that with NPH insulin. Injection site reactions, most of which are minor, are most common adverse events with insulin glargine, and are seen 3-4% of patients. Evidence to date shows that insulin glargine is no more immunogenic than NPH insulin.

Clinical experience with insulin glargine in type 1 and type 2 diabetes

A number of studies have investigated the efficacy and safety of insulin glargine in comparison with NPH. Short-term, randomized parallel studies of insulin glargine vs NPH insulin have demonstrated that, insulin glargine effords equivalent improvment in HbA1c, but significantly lower fasting plasma glucose levels compared with NPH insulin (7). In other short-term study comparing NPH insulin with insulin glargine, baseline to endpoint changes in HbA1c were also smiliar in the two treatment groups. The reduction in fasting blood glucose was significantly greater with insulin glargine (8).

A longer study comparing insulin glargine with NPH insulin in combination with lispro also showed no significant betweeen treatment differences in baseline to endpoint reductions in HbA1c, however treatment with insulin glargine resulted in significantly greater baseline to endpoint reductions in fasting plasma glucose. In this study, similar levels of overall symptomatic and nocturnal symptomatic hypoglycaemia were reported in both groups (9).

In other long-term study insulin glargine was compared with NPH insulin, in combination with human regular insulin (10). Once again, baseline to endpoint decreases in HbA1c were similar in both groups, but the baseline to endpoint reduction in fasting plasma glucose was significantly greater with insulin glargine than with NPH insulin. The incidences of symptomatic, nocturnal or severe hypoglycaemia were significantly lower in the insulin glargine treatment group compared with NPH insulin treatment group.

In addition to studies carried out in adult type 1 diabetics, comparative studies of insulin glargine with NPH insulin have also been carried out in pediatric patients with type 1 diabetes. A small study of children with type 1 diabetes randomized to receive either insulin glargine or NPH insulin combained with prandial regular insulin demonstrated more stable overnight glucose control with insulin glargine (11). In a larger study, 349 children with type 1 diabetes were randomized to receive either insulin glargine of NPH insulin, in combination with prandial human regular insulin (12). A significantly greater decrease in fasting blood sugar levels was observed in insulin glargine group than NPH insulin treatment group. Table 1 shows summary of clinical studies in patients with type 1 diabetes (NPH insulin vs insulin glargine).

There are a number of published studies compairing insulin glargine with NPH insulin in combination with either OHAs or prandial insulin in patients with type 2 diabetes. A 52 week study compairing insulin glargine with NPH insulin as an adjunct to

Table 1. Summary of clinical studies in patients with type 1 diabetes (NPH vs Glargine).

			Change at endpoint vs baseline		Incidence of hypoglycaemi		
Study design	n	Duration	HbA1c %	FPG mmol/L	All (%)	Nocturnal (%)	Reference
Partially blinded, randomized, paralel	333	4 weeks	-0.25	-2,22	79	36	
NPH (once or twice daily) vs GLAR			GLAR 30	GLAR 30	GLAR 30	GLAR 30	Pieber et al.
once daily (30 or 80 µg/mLzinc)			vs	vs	vs	vs	2000
plus prandial regular insulin			-0.15	-1.61	73	36	
			GLAR 80	GLAR 80	GLAR 80	GLAR 80	
			vs	vs	vs	vs	
			-0.03	0.01	79	61	
			NPH	NPH	NPH	NPH	
Open label, randomized, parallel	619	16 weeks	- 0.1	- 2..2	90.6	69	
NPH (once or twice daily) vs GLAR			GLAR	GLAR	GLAR	GLAR	Raskin et al.
(once daily) plus prandial insulin lispro			vs	vs	vs	vs	2000
			- 0.1	- 0.7	90.6	63.1	
			NPH	NPH	NPH	NPH	
Open label, randomized, parallel	534	28 weeks	- 0.16	- 1.67	39.9	18.2	
NPH (once or twice daily) vs GLAR			GLAR	GLAR	GLAR	GLAR	Ratner et al.
(once daily) plus prandial insulin			vs	vs	vs	vs	2000
			- 0.21	- 0.67	49.2	27.1	
			NPH	NPH	NPH	NPH	
Open label, randomized,	349	6 months	0.28	-1.29	78.9	12.6	
NPH (once or twice daily) vs GLAR			GLAR	GLAR	GLAR	GLAR	Schober et al.
(once daily) plus prandial reg insulin			vs	vs	vs	vs	2001
(children 5-16 years)			0.27	- 0.68	79.3	17.7	
			NPH	NPH	NPH	NPH	

OHAs demonstrated a comparable baseline to endpoint change in HbA1c in two treatment groups, but significantly lower pre and post dinner blood glucose levels at the endpoint with insulin glargine. The incidence of nocturnal hypoglycaemia was significantly lower with insulin glargine than with NPH insulin (13). In another study of patients with type 2 diabetes treated previously with insulin only, patients were randomized to receive either insulin glargine or NPH insulin in combination with prandial regular insulin (14) Glycaemic control archieved with insulin glargine or NPH insulin was similar to that achieved with NPH insulin treatment. While the incidence of symptomatic hypoglycaemia was similar in both groups, the incidence of nocturnal hypoglycaemia was significantly lower with insulin glargine.

In conclusion, clinical experience with insulin glargine in type 1 and type 2 diabetes demonstrated that glycaemic control equivalant to that of NPH insulin. Each of the studies summarized above shows a benefit for insulin glargine over NPH insulin with respect to fasting plasma glucose or occurence of hypoglycaemia particularly nocturnal episodes.

Insulin Detemir

The mo st recent strategy has been to acylate fatty acid residues to the insulin molecule, enabling the resulting analogue to bind albumin. Insulin detemir has been engineered to add a fatty acyl chain on to the lysine residue of the B-chain, so as to increase binding to albumin. The duration of action is extended due to continued release of insulin that has been bound to circulating albumin (15).This analouge exists in the presence of zinc and phenol, like native insulins, predominantly in the hexameric state. The fatty acid side-chain contributes to provide aggregation of hexamers, which can contribute to delay hexamer dissociation and absorption. In the monomeric state, the 14-C fatty acid chain attached to position B29 binds to binding sites on albumin. Because only the free fraction of insulin detemir is biologically active, albumin binding and the ensuing slow dissociation of the analogue from the albumin further prolong the blood glucose-lowering action. The soluble formulation ensures a homogenous concentration, with no need for agitation before administration. Clinical trials in healty subjects suggest that insulin detemir has a

less-prounounced peak of action and lower intra-subject variations in pharmacokinetic parameters compared with NPH insulin (16,17). Thus, insulin detemir may provide more consistent insulin levels and more predictable glucose control than NPH because of lower absorption variability. The dose requirment of insulin detemir appers to be somewhat higher than that of NPH compared on a molar basis (18). As mentioned above, an increased binding time at the insulin receptor or increased affinity for IGF-I receptors may increase the mitogenic potential of the analogue. In the case of insulin detemir, the ratio of insulin receptor affinity to IGF-1 receptor affinity is not increased relative to insulin receptor affinity, and this is reflected in a low mitogenic potency in human cancer cell line (19) (Table 2).

Importantly, the binding of insulin detemir has been shown to be independent of the binding of drugs in the two major binding pockets that are located in domains IIA and IIIA of the albumin molecule. Thus, insulin detemir is unlikely to be involved in clinically significant drug interactions at the albumin binding level (18).

Clinical Experience with Insulin Detemir

The pharmacokinetic and pharmacodynamic properties of insulin detemir (0.3 and 0.6 U/kg) and NPH insulin (0.3 and 0.6 U/kg) were compared in ten healthy volunteers in a randomized, double blind, cross-over, placebo controlled glucose clamp study. The data indicated a clear dose-response relationship for both compounds. The AUC for glucose infusion after treatment with insulin detemir however, was only 36% (0.3 U/kg) and 24% (0.6 U/kg) of that observed with corresponding doses of NPH insulin (19).

During a double-blind, six-period, crossover study designed to investigate the pharmacokinetic profile and duration of action of insulin detemir, type 1 patients were randomized to one dose of NPH (0.3 U/kg) and five doses of insulin detemir (0.1, 0.2, 0.4, 0.8 and 1.6 U/kg). The study was carried out as a 24-h isoglycaemic clamp and the results showed that, based on AUC GIR, a dose of between 0.2 and 0.4 U/kg insulin detemir was comparable to 0.3 U/kg NPH insulin. The profiles obtained with insulin detemir, however, were flatter and less variable than that the NPH profiles (20).

Insulin detemir and NPH insulin were invastigated in an open-label, multicenter, randomized crossover trial in type 1 diabetic individuals aimed at comparing the blood glucose lowering effects of the two compounds and evaluating the two treatments with to intra-individual variations of fasting blood glucose level, indicence of hypoglycaemia, dose requirements and safety. The results indicate that insulin detemir may provide a more predictable fasting blood glucose level with lower intra-individual variation and reduced risk of hypoglycaemia compared with NPH insulin. In addition, insulin detemir was as effective as NPH insulin in maintaining glycaemic control when administered at a 2-3 fold higher dose (21,22).

Insulin detemir has entered phase III and IV trials in several sites worldwide. Insulin detemir and NPH insulin have been compared in a 6 month, multicenter, multinational, open-label, randomized, parallel, safety and efficacy trial. Type 1 diabetes patients (n=447) were treated either insulin detemir or NPH insulin, in combination with insulin aspart. Both treatments demonstrated equivalent overall glycaemic control as measured by HbA1c and fasting plasma glucose. Intra-individual variation in fasting blood glucose was slightly, but not significantly, less with insulin detemir. The safety profiles of the treatments were similar. The relative risk of having a hypoglycaemic episode was 20% lower in the insulin detemir treated group (23,24).

Table 2. Receptor Binding, Metabolic and Mitogenic Potency of Basal Insulin Analogues.

	Insulin receptor affinity	Metabolic potency	IGF-1 receptor affinity	IGF-IR/IR affinity	Mitogenic potency (Saos/B10 cells)
Human Insulin	100	100	100	1	100
Insulin Glargine	86 ± 3	60 ± 3	641 ± 51	7.5	783 ± 13
Insulin Detemir	~18 - 46	~27	16 ± 1	0.9	~11

In an other study insulin detemir and NPH insulin were compared in 288 patients. After a total 12 months, in which 252 patients completed the trial, insulin detemir and NPH insulin demonstrated similar overall glycaemic control with insulin detemir treated patients at a lower risk of hypoglycaemia. A weight loss of 0.3 kg in the insulin detemir group was observed (25).

In a other 6- month multinational, open parallel group comprasion study conducted at 46 centers in five countries and included 448 patients with type 1 diabetes randomised to insulin detemir or NPH insulin. Teatment with insulin detemir resulted in more predictable glycaemic control, with smoother plasma glucose profiles than NPH insulin and a significant reduction in risk of hypoglycaemia. The reduction in body weight with insulin detemir is a potential additional advantage (26).

Recently, a 6-month, prospective, randomised, open-label, controlled, parallel-group trial conducted at 92 sites in Europe and Australia. The trial populations included patients with type 1 diabetes for at least 1 year, aged > 18 years with HbA1c <12% already taking basal-bolus treatment with an intermediate –or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin. Patients were randomly assigned to 6 months of treatment with insulin detemir or NPH at bedtime in combination with human insulin with main meals. Main outcome measures were blood glucose control as assessed by HbA1c, fasting plasma glucose, 9-point self-monitored blood glucose profiles, hypoglycaemia, weight gain and adverse events. Administration of insulin detemir at bedtime resulted in lower fasting blood glucose levels with less day-day variability than NPH insulin, combined with an overall reduction in the risk of nocturnal hypoglycaemia (27).

A 18-week study compared the efficacy and tolerability of two types of basal-bolus therapy, using either the soluble long-acting basal insulin analogue, insulin detemir, in combination with the rapid-acting analogue, insulin aspart or NPH insulin in combination with mealtime regular human insulin. Basal-bolus therapy using insulin detemir / insulin aspart offers a better balance of control and tolerability than with NPH insulin / regular human insulin. The low variability and more physiological action profiles generated with these insulin analogues resulted in improved glycaemic control with lower risk of hypoglycaemia and no concomitant body weight increase (28).

In addition to studies carried out in adult type 1 diabetics, comprative study of insulin detemir with NPH insulin have also been carried out in pediatric patients with type 1 diabetes. In a single center, open-label, randomized, crossover trial included children (aged 6-12 years), adolescents (aged 13-17 years) and adults (aged 18-65 years) of both sexes. Subjects were given single doses of 0.5 U/kg insulin detemir or 0.5 U/kg NPH insulin. The data suggest that insulin detemir can be used in children and adolescents with type 1 diabetes using titration guidelines similar to tose 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 (29).

At present, there is only one study compared insulin detemir with insulin glargine and NPH insulin in type 1 diabetes. In this randomized, double-blind study included 54 patients with type 1 diabetes. Each subject received for single sc doses of 0.4 U/kg of either insulin detemir,insulin glargine or human NPH insulin under euglycaemic glucose clamp conditions (target blood glucose concentration 5.5 mmol/L) on four identical study days. The pharmacodynamic (glucose infusion rates) and pharmacokinetic (serum concentration of insulin detemir, human insulin and insulin glargine) properties of the basal insulin preprations were recorded for 24 h postdosing. Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine. The results also suggest that insulin detemir has a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine (30).

Conclusions

The importance of blood glucose control in order to minimize long-term diabetic complications is unquestinable. Plasma glucose concentrations in healthy subjects remain within a narrow range which might suggest that fluctiations in glucose

levels have negative consequences. While no treatment is at present able to perfectly reproduce a physiological insulin profile, several insulin analogues have proved promissing. In fact, the perception by many patients who use long-acting insuin analogue is positive as far as their quality of life is concerned and these compounds seem to be instrumental in minimizing the side effects of insulin therapy (risk of nocturnal hypoglycaemia or problems with body weight control). In objective efficacy terms, however, the potential of the drugs to improve metabolic control still needs to be addressed. This is particularly relevant in pediatric diabetologia.

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