Review

INSULIN GLARGINE

Umesh Dashora, Vandana Dashora

ABSTRACT

Insulin glargine is a new designer insulin with a peak-less and constant profile of action from two hours to over 24 hours (hrs). This property is highly suitable for providing basal insulin requirement to patients with diabetes. Glargine leads to greater reduction in fasting plasma glucose levels and significant reduction in hypoglycemic episodes. It is generally safe. However, the recent observations regarding increased mitogenicity in malignant cell lines and a tendency to cause progression of diabetic retinopathy, needs further clarifications.

KEY WORDS: Glargine insulin; Basal; Hypoglycemia; Fasting glucose; Mitogenicity; Retinopathy.

INTRODUCTION

The new long-acting insulin analogue, glargine (Lantus, Avantis Pharma) was approved for use in patients with type 1 and type 2 diabetes by the US food and Drug Administration in April 2000, and by the European Agency for the Evaluation of Medicinal Products in June 2000.

PHARMACOLOGICAL CHARACTERISTICS

Insulin glargine is produced by substituting amino acid glycine for aspargine at position A21 of the A-chain of human insulin and by adding two arginine molecules to the NH_2 terminal end of the B-chain of human insulin, using recombinant DNA technology.

It has an isoelectric point at pH 6.7, in contrast to the native molecule of insulin, that has an isoelectric pH of 5.4. This makes glargine insulin soluble at acidic pH and less soluble at the physiological pH. It is supplied as clear, colourless solution at acidic pH.

Upon subcutaneous injection, the acid in the vehicle is neutralised and glargine precipitates, thereby delaying its absorption and prolonging its action.

TIME ACTION PROFILE

Heinman et al (1) have published the results of single-dose, double blind, crossover, euglycemic clamp studies in healthy, male, volunteers and compared the time-action profile of subcutaneously injected glargine, NPH insulin and placebo. They have shown an essentially peakless profile of action, with its onset of action at 2-4 hrs and a duration over 24 hrs. NPH on the other hand resulted in a substantial peak in action at 4 hrs, with a subsequent decline in activity through the duration of the 30-hrs study. They concluded that insulin glargine provides a flatter metabolic profile, than NPH insulin. Insulin receptor binding of HOE 901 or glargine insulin is only 50% of that of human insulin and this led to higher circulating levels of insulin and therefore equivalent in vivo activity in some studies (2,3) This may be an advantage, when providing basal insulin requirements to patients with diabetes.

In an another study, NPH and ultralente insulin exhibited a peak concentration and action (at 4.5±0.5 and 10.1±1hrs, respectively) followed by waning. Glargine had no peak, but had a flat concentration/action profile mimicking continuous subcutaneous insulin infusion (CSII). Inter-individual variability (calculated as differences in SD of plasma insulin concentrations and glucose infusion rates in different treatments), was lower with glargine than with NPH and ultralente ($P<0.05$), but was similar with glargine and CSII (NS). In conclusion, NPH and ultralente are both peak insulins. Duration of action of ultralente is greater, but inter-subject variability is also greater than that of NPH. Glargine is a peakless insulin, its action lasts for nearly 24hrs. It has a lower inter-subject variability than NPH and ultralente and it closely mimics CSII, the gold standard of basal insulin replacement (4).

CLARITY OF SOLUTION

That glargine insulin is a clear solution, maybe a distinct clinical advantage in daily clinical use. It has been shown that suspensions like NPH insulin, are often not shaken enough by the patients, before administration (5). It goes without saying, that because it is not necessary to shake glargine insulin before injection, it may have a lower intra-individual variability of the metabolic effect induced. It is also likely that a clear solution may show a more even distribution in the subcutaneous

Specialist Registrar, Diabeties and Endocrinology RVI, Newcastle upon Tyne. UK.

tissue, before it precipitates, and thereby further reduces variability. However, when NPH is shaken thoroughly before administration, the variation in its metabolic effect is not significantly different from glargine (6). Some recent trials, however, have shown reduced variability of fasting blood glucose and a lower risk of hypoglycemic episodes with glargine as compared to NPH insulin (7,8).

LOW RISK OF HYPOGLYCEMIA, BETTER FASTING GLUCOSE

Initial results of the US study group of insulin glargine have been recently published (9). In this paper, Ratner et al describe the results of a large, randomised, prospective, 28 week trial, of insulin glargine versus NPH insulin (10). Insulin glargine was well tolerated without evidence of antibody formation and with only minimal injection site reactions (pain). Insulin glargine demonstrated a significantly greater reduction in fasting plasma glucose (FPG) levels. The decrease in FPG levels oecurred almost immediately (week 1) with insulin glargine and were maintained for the duration of the study. In contrast, decreases in FPG levels with NPH insulin occurred gradually, according to protocol driven insulin adjustments, and were maximised at week 28. After the initial titration phase of two months., there was also a significant reduction in hypoglycemia, including nocturnal and severe hypoglycemic episodes.

No change in overall glycemia control or in HbA_{1c} has yet been observed with substitution of glargine for NPH (9,11,12). However, In studies of type 1 diabetes (13,14), glargine was given with human regular insulin at mealtime. Its use could be optimised by a regimen of insulin glargine once daily with short acting insulin analogue at meal times, in type 1 diabetics. Such a regimen would be comparable to CSII or MSI (15).

In a study from Oxford (16), NPH insulin led to higher free insulin overnight, whereas the use of glargine led to lower free insulin levels. This resulted in a more stable blood glucose control. This might be beneficial, especially in terms of prevention of nocturnal hypoglycemia. This study included children on long-acting insulin, as a part of a three-injection regimen. Normally, the target for adjusting the evening long-acting insulin dose, is the fasting blood glucose measurement of the following morning. In the glargine group, the mean fasting blood glucose was 6.8mmol/l. When using the regimen of NPH insulin and regular insulin, we might be relucant to increase the evening NPH insulin based on these readings, because doing so might increase the already high risk of nocturnal hypoglycemia. However, a more stringent titration might be possible with glargine, because of the lower risk of hypoglycemia.

In an another study, Jarvinen (17) et al, have shown that bed time insulin glargine leads to less nocturnal hypoglycemia and better post-dinner glucose control as compared with bed time NPH insulin, during insulin combination therapy in type 2 diabetes. Oral agents were continued in these patients without change. The data also suggests that the target FPG can be lower for insulin glargine than for NPH.

In an another recent study, Owens et al (14) have shown that fewer episodes of hypoglycemia were experienced with glargine than with NPH, especially at night (65.1 versus 101.2 episodes per 1000 patient years). Glargine was also less immunogenic than NPH insulin, in the same study. These differences did not however, result in an insulin sparing effect or in differences in glycemic control, in the face of similar insulin doses. The clinical significance of insulin antibodies remains controversial.

In a 16 week comparison of glargine and NPH, used with insulin lispro in type 1 diabetics, as basal-bolus therapy, glargine once a day, appears to be as safe and at least as effective as NPH once or twice a day, in maintaining glycemic control (18). The only differences in the safety profile of insulin glargine and NPH insulin was that a disproportionate number of insulin glargine patients reported pain at the injection site. This could be related to the acidic pH of glargine or could be because of a reporting bias.

GLARGINE VERSUS OTHER LONG ACTING INSULINS

Some of the articles cited above, leave the reader with a sense of promise, but it remains to be proved that glargine is definitely superior to the other long acting insulins. Till now glargine has been shown to be better at producing lesser hypoglycemic episodes, however the reduction in HbA_{1c} is not superior. This situation may be similar to the situation with lispro insulin, where the data showing improvement in HbA_{1c} (19,20) lagged behind the data regarding hypoglycemia reduction. It may be some time before the pharmacological advantages of glargine insulin can be translated into therapeutic triumphs.

GLARGINE IN DIFFICULT PATIENTS

In a small study at North Carolina (21), researchers identified subjects who had done poorly on multiple injection regimens, despite maximal interventions. These subjects were then put on glargine insulin. Glargine improved the glycemic control in these subjects and the most dramatic response was seen in patients who could not achieve glycemic control targets, without unacceptable levels of hypoglycemia, despite multiple attempts with various regimens, involving essentially all possible combinations of available insulin formulations. Moreover, the control of these patients definitely worsened when glargine insulin was withdrawn at the conclusion of the study.

POTENTIAL BENEFITS

Based on the theoretical benefits and available data, it looks like glargine will benefit patients who have difficulty with glycemic control. Many other potential uses of glargine will require specific study before they can be widely considered, such as its use in pregnancy and as a form of immunomodulatory therapy for the prevention of autoimmune diabetes.

POTENTIAL DIRECTIONS

It is maybe worthwhile to compare glargine with human ultralente insulin. As there are strong proponents and opponents of ultralente therapy, it certainly would be an interesting aspect to work on.

In some European countries, patients are accustomed to twice a day injections of NPH insulin. Therefore, it would be useful to compare the effect of a once a day injection of glargine with those of a twice a day injections of NPH insulin in appropriate doses.

A WORD OF CAUTION IS INSULIN GLARGINE A SAFE ANALOGUE?

Mutagenic Potential

Development of mammary tumours in a strain of mice given the short acting B10-Asp insulin analogue, raises the possibilities of the mitogenic potential of every new insulin product. Changes in insulin structure may alter the way it interacts with insulin and insulin growth factor receptors. Insulin glargine has 50-60% the affinity of insulin for the insulin receptor, and in-vitro potency of 60%, but an equivalent in- vivo potency, because the plasma concentrations reached are twice those of insulin (3). Insulin glargine dissociated at only 10-20% of the rate of human insulin. Like the insulin analogue Asp B 10, insulin glargine has up to six-fold greater affinity for IGF-1 receptors than human insulin (22). In cell lines with predominantly high expression of IGF-1 receptors, such as the human osteosarcoma cell line (Saos/B10) and human epithelial cells (HMEC), a close relation between IGF-1 receptor affinity and mitogenic potency has been described (23).However, since only the Asp B10 insulin analogue caused mammary tumours when given in high doses (12.5-200 U/kg) to rats, whereas insulin glargine given to rats and mice at lower doses (2-12.5 U/kg) for up two years did not, the carcinogenic effect is not substance specific. This suggests that a long residence time on insulin receptor may be an important component of the enhanced mitogenicity of the Asp B 10 insulin analogue. Experiments using cell-lines expressing mainly insulin receptors (rat fibroblasts) (21) and human mammary epithelial cell lines have not shown increased mitogenicity, as measured by thymidine incorporation with insulin glargine. Clinical relevance of the recent observation by Kurtzhals et al (22), of increased mitogenicity of insulin glargine as compared with human insulin, in a malignant cell-line, remains to be determined. Faced with safety concerns, on April 12, 2000, the European Agency for the evaluation of medical products, issued a draft concepts paper asking to consider appropriate procedures for the non-clinical assessment of carcinogenic potential of human insulin analogues (www.eudra. org/humandocs/ PDFs/SWP/078100en. pdf accessed Nov 2,2000).

Retinopathy Progression

IGF 1 signalling has been implicated in the regulation of vascular endothelial growth factor dependent retinal neovascularisation (24). This might explain the observation of a three-grade progression of retinopathy (according to a scale used in the Early Treatment Diabetic Retinopathy Study) in some patients with type 2 diabetes treated with insulin glargine. However, review of retinopathy data and the absence of optic disc swelling during the studies (the most common ocular adverse effect of IGF-1 treatment), led an independent panel, convened by Savants pharmacy, to conclude that this finding was not related to therapy with insulin glargine. Nevertheless, the US Food and Drug Administration, stated in its letter of approval for insulin glargine, that Avantis pharma is committed to do a phase 4 study to compare the proportion of patients with type 2 diabetes with a 3 step or more progression of retinopathy, during treatment with once daily insulin glargine or twice daily NPH, with specified dates (25).

In keeping with human nature, we are generally eager to adopt newly released products. However, it is our responsibility, as professionals, to be judicious in exploring and advising about all new drugs and technologies. For a while it would be very important to report any unexplained event occuring after the use of any new product, like glargine insulin. We might like to report them to both the pharmaceutical industry and to the FDA or any other relevant national body. On-line reporting is also available at http:// www.fda.gov/medwatch/. Phone No 800-FDA-1088 and Fax 800-FDA-0178.

Care must be taken to educate the patient about the danger of mixing glargine with other insulin formulations, as glargine will precipitate instantly. We should also review the rules of sick-day management and the management of both hyper and hypoglycemia, while starting any new therapy, and glargine should be no exception. It would also be prudent to encourage more frequent monitoring, particularly at bedtime and in mid sleep, for at least a week after switching formulations.

REFERENCES

1. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedladm, Heise T. Time action profile of the long-acting insulin analog insulin glargine (HOE 901) in comparison with those of NPH insulin and placebo. Diabetes Care, 2000; 23:644-9

2. Drejer K, Kruse V, Larsen DU, Hougaard P, Bjorn S, Gameltoft S. Receptor binding and tyrosine kinase activation by insulin analogues with extreme affinities studied in human hepatoma Hep G2 cells. Diabetes, 1991; 40:1488-95

3. Bolli GB, Di Marchi RD, Park GD, Pramming S Koivisto VA. Insulin analogues and their potentials in the management of Diabetes Mellitus. Diabetologia 1999; 42:1151-67

4. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000; 49(12): 2142-8

5. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of Neutral Protamine Hagedorn (NPH) insulins in pens. Lancet 1999; 354: 1604-7

6. Scholtz HE, van Niekerk N, Meyer BH, Rosenkranz B. An assessment of the variation in the pharmacodynamics (glucose lowering effect) of HOE 901 compared to NPH and ultralente human insulins using the euglycemic clamp techinque. Diabetologia 42 (suppl.l) 1999; A235

7. Ratner RE, Hirsch IB, Mecca TE, Wilson CA. Efficacy and safety of insulin glargine in subjects with type 1 diabetes: a 28 week randomised NPH insulin-controlled trial. Diabetes 48 (suppl.l) 1999: A100

8. Rosenstock J, Schwartz S, Clark C, Edward M, Donley D: Efficacy and safety of HOE 901 (insulin glargine) in subjects with type 2 diabetes: A 28 week randomised NPH insulin-controlled trial. Diabetes 1999; 48 (suppl 1): A100

9. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US study group of insulin glargine in type 1 diabetes. Diabetes Care, 2000; 23: 639-43

10. Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European study group of HOE 901 in type 1 diabetes. Diabetes Care, 2000; 23(2): 157-62

11. Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. A four-week randomised, NPH insulin controlled trial. Diabetes 1999; 47(suppl.l): A62

12. Yki-Jarvinen H, Dessler A, Ziemen M, Study Group H0E901/3002. Comparison of insulin Glargine (HOE 901) vs. NPH during 1 yr of insulin combination therapy in type 2 diabetes. Diabetes 2000; 49 (suppl. 1): A130

13. Lepore M, Kurzhals R, Pampanelli S, Giuseppe C, Fanelli C, Bolli GB: Pharmacokinetics and dynamics of s.c. injection of the long-action insulin glargine (HOE 901) in type 1 diabetes melltius. Diabetes 1999; 48 (suppl. 1): A 97.

14. Owens DR, Barnett A. Designer insulins: Have they revolutionalized insulin therapy? *In*: Batterdge JD, *ed*. Diabetes-current perspectives London: Martin Duniitz. 1999.

15. Bolli GB, Fanelli CG, Porter PA: Nocturnal blood glucose control in type 1 Diabetes mellitus. Diabetes Care 1993; 17; 78-80.

16. Mohn A, Strang S, Wernicke-Panten K, Lang AM, Edge JA, Dunger DB. Nocturnal glucose control and free insulin levels in children with type 1 diabetes by use of the long acting insulin HOE 901 as part of a three-injection regimen. Diabetes Care, 2000; 23(4): 557-9

17. Yki-Jarvinen H, Dessler A, Ziemen M. Less Nocturnal hypoglycemia and better post-dinner glucose control with bed time insulin glargine compared with bed time NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 study group. Diabetes Care, 2000; 23 (8): 1130-6

18. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care, 2000; 23(11): 1666-71.

19. Zinman B, Tildesley H, Chiasson J, Tstrack T: Insulin lispro in CSII: Results of a double-blind cross over study. Diabetes 1997; 46: 440-3.

20. Lalli C, Ciofetta M, Del Sindaco P, Tor E, Pampanelli S, Compagnucci P, Cchini MG, Bartocci L, Brunetti P, Bolli GB. Long-term intensive treatment of type 1 Diabetes with the short-acting insulin Humalog lispro in variable combination with NPH insulin at mealtime. Diabetes 1999; 22: 468-77

21. Buse J. Insulin Glargine (HOE 901). Diabetes Care 2000; 23; 576-8

22. Kurtzhals P, Schaffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, Trub T. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes 2000; 49(6); 999-1005

23. Slieker LJ, Brooke GS, DiMarchi RD, Flora DB, Green LK, Hoffmann JA, Long HB, Fan L, Shields JE, Sundell KL, Surface PL, Chance RE. Modifications in the B10 and B26-30 regions of the B chain of human insulin alter affinity for the human IGF-1 receptor more than for the insulin receptor. Diabetologia, 1997; 40; Suppl. 2: S54-61

24. Smith LEH, Shen W, Peruzzi c, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. Nat. Med, 1999; 5: 1390-5

25. Berger M. Safety of Insulin glargine. Lancet, 2000; 356: 2013