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Insulin Glargine: A Long-acting Insulin for Diabetes Mellitus

Summary

- ✓ **Insulin glargine is a once-daily, biosynthetic, human insulin analogue.**
- ✓ **Some trials show that in patients with type 1 diabetes mellitus, insulin glargine offers an advantage in blood glucose control compared with NPH insulin.**
- ✓ **There is some evidence of decreased nocturnal and symptomatic hypoglycemia in patients receiving insulin glargine compared with those receiving NPH insulin, but there are no significant differences in the incidence of severe hypoglycemia.**
- ✓ **Insulin glargine is approved for use in Canada, but it has not yet been marketed.**

The Technology

Upon subcutaneous injection, the acidic insulin glargine solution (Lantus™; HOE 901) is neutralized. This results in the formation of microprecipitates, which provide a constant release of insulin glargine without a pronounced peak over a 24-hour period.[1]

Regulatory Status

Lantus™ is administered once daily subcutaneously in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus (DM) who require long-acting insulin control of hyperglycemia.[1] Insulin glargine is available in Germany, the US and the UK.[2] Health Canada granted a notice of compliance to Aventis Pharma Inc. on April 3, 2002,[3] but it has not been launched in Canada (Luc Sauriol, Aventis Pharma Canada, Montreal: personal communication, 2003 October 8).

Patient Group

DM is a disorder of defective insulin action. About two million Canadians have DM;[4] approximately 60,000 new cases are diagnosed annually.[5] About 10% of the population with DM have type 1, which results from insufficient insulin production.[4] These patients require exogenous insulin. Type 2 DM is a result of insulin resistance and variable insulin production. These patients require oral hypoglycemic agents and some may use exogenous insulin.

Current Practice

Glycemic control can be monitored using glycosylated hemoglobin A_{1c} (HbA_{1c} or A_{1c}) and fasting plasma glucose (FPG) or fasting blood glucose (FBG). A_{1c} reflects control over the preceding three to four months, while self blood glucose monitoring (SBGM) measures control in the short term.

The Diabetes Control and Complications Trial (DCCT)[6] shows that maintaining near-normal glycemia using insulin as measured by A_{1c}, reduces the occurrence of serious diabetic complications in type 1 DM. Multiple insulin injections are needed to attain such levels. In basal-bolus regimens, a short-acting insulin (e.g. regular, lispro) before each meal and a long-acting, basal insulin (e.g. neutral protamine Hagedorn (NPH), ultralente) are administered.

The Evidence

Among eight trials identified,[7-14] five are published in abstract form.[7,9-12] These trials compare insulin glargine with NPH. The effects on long-term diabetic complications cannot be assessed because the trials do not last long enough. All trials are open-label because NPH is cloudy whereas insulin glargine is clear.

Table 1: Randomized trials comparing once-daily insulin glargine with NPH insulin in patients with type 1 DM

Trial	Insulin glargine (mean baseline ± SD)	NPH Insulin (mean baseline ± SD)	Insulin Glargine (mean change from baseline to endpoint)	NPH Insulin (mean change from baseline to endpoint)	p, Insulin Glargine versus NPH Insulin
Raskin *et al.*,‡[14] 16 w, n=619					
Mean A_{1c} (%)	7.6±1.2	7.7±1.2	-0.1	-0.1	NS
Mean FBG (mmol/L)	9.7±3.3	9.6±2.6	-1.7	-0.6	0.0001
Ratner *et al.*,‡[13] 28 w, n=534					
Mean A_{1c} (%)	7.7±1.2	7.7±1.1	-0.16	-0.21	NS
Mean FBG (mmol/L)	9.2±2.7	9.7±3.0	-1.1	-0.9	NS
Garg *et al.*,†[9] 28 w, n=45					
Mean A_{1c} (%)	NR	NR	NR	NR	NR
Mean FPG (mmol/L)	11.4±1.0	10.1±1.1	-3.3	-0.8	NS
Hershon *et al.*,†[12] 28 w, n=394					
Mean A_{1c} (%)	Overall 7.7		NR	NR	NR
Mean FBG (mmol/L)	Overall 9.3		-1.38	-0.8	0.014
Fulcher *et al.*,*[7] 30 w, n=125					
Mean A_{1c} (%)	9.18±11.2	9.72±1.3	-1.04	-0.51	0.009
Mean FBG (mmol/L)	11.2±3.5	11.4±4.1	-3.46	-2.34	0.003
Home *et al.* ‡[11] 28 w, n=585					
Mean A_{1c} (%)	7.9±1.2	8.0±1.2	0.21	0.1	NS
Mean FBG (mmol/L)	9.3±2.7	9.2±2.4	-1.17	-0.89	NS
Porcellati *et al.*,§[10] 52 w, n=121					
Mean A_{1c} (%)	NR	NR	-0.5	-0.1	<0.05
Mean FBG (mmol/L)	NR	NR	NR	NR	NR
Rosetti *et al.*,§[8] 12 w, n=51					
Mean A_{1c} (%)	6.8±0.2, 7.0±0.2	6.9±0.1	-0.4, -0.4**	0.1	<0.04
Mean FBG (mmol/L)	NR	NR	NR	NR	NR

*NPH once daily, †NPH twice daily, ‡NPH once or twice daily, §NPH four times daily, **dinner insulin glargine versus bedtime insulin glargine versus NPH insulin, w=week, NS=not significant (p>0.05), NR=not reported

Three trials report significantly greater reductions in A_{1c}.[7,8,10] There are significantly greater FBG reductions with insulin glargine compared with NPH insulin treatment in three trials.[7,12,14]

Of three trials[15-17] that involve 474 children and adolescents and last six to 12 months, two are published in abstract form.[16,17] There are no significant differences in A_{1c} between groups. Two trials report increased A_{1c} levels.[15,16] There is some evidence of lower FBG levels with insulin glargine treatment.[15,17]

Adverse Effects

No significant differences in the incidence of severe hypoglycemia are reported in the adult trials that last more than 12 weeks. Some trials show significant decreases in nocturnal[7,8,10,13] and symptomatic[12] hypoglycemia with insulin glargine compared with NPH insulin. More patients experience pain or injection site reactions with insulin glargine compared with NPH insulin,[13,14] presumably because of the acidity of the delivery vehicle.[18]

Administration and Cost

Insulin glargine is supplied as 100 IU/mL in 10 mL vials and 3 mL cartridges.[1] Its administration with another insulin requires two separate injections.[1]

In the US, the average wholesale price of the 10 mL vial is $46.99 US.[19] No Canadian pricing is available. The UK's National Institute for Clinical Excellence projects the yearly incre-

mental cost-effective ratios for insulin glargine versus NPH to be between £3,500 to £16,000 per quality adjusted life year in type 1 DM.[20]

Concurrent Developments

The slow-release insulin produced by fatty acid acylation, insulin detemir (NN304), is undergoing phase III trials. A 24-hour, controlled-release formulation of human insulin is being investigated.[21]

Rate of Technology Diffusion

Patients report more treatment satisfaction with insulin glargine than with NPH[22] and some may switch from twice-daily NPH to once-daily insulin glargine. Patient and physician experience with NPH insulin dosing may not be transferable to insulin glargine.[23] As a result, doses may need to be readjusted.

The potential increased cost and lack of long-term efficacy and safety data could limit the diffusion of insulin glargine.

Trials involving patients with type 2 DM indicate no improvement in glycemic control and a lower incidence of nocturnal hypoglycemia. A phase IV evaluation will be conducted to assess whether insulin glargine is involved in the development of retinopathy.[24]

Implementation Issues

Insulin glargine is a treatment option for patients with type 1 DM. The evidence supporting its use over NPH insulin is limited, so the use of the drug versus alternatives may be limited to patient and physician preferences.

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