Insulin Glargine (Lantus), The Peakless Long-acting Basal Insulin: Its Clinical Application in Type 2 Diabetes

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Tight blood glucose control is crucial in the prevention of vascular complications in type 2 diabetes as evident from the United Kingdom Prospective Diabetes Study (UKPDS). With increasing disease duration, optimal glycaemic control is seldom achieved with oral anti-diabetic therapy alone. This is due to the progressive pancreatic β-cell failure in the natural history of type 2 diabetes. Many type 2 diabetic patients will ultimately require insulin. However, many Hong Kong Chinese type 2 diabetic patients are either poorly controlled (HbA1c > 8.0%) or suboptimally controlled (HbA1c 7.0-8.0%) despite maximum oral anti-diabetic therapy. Initiation of insulin therapy is often hampered by the perceived complexity, the belief that insulin is not effective for type 2 diabetes and fear of hypoglycaemia. In reality, application of insulin as outpatient is simple and practical. The availability of new insulin analogues allows greater physiological control with fewer episodes of hypoglycaemia.

Basal insulin: limitations of conventional preparations

In the non-diabetic individuals, there is a constant pulsatile secretion of insulin to maintain the blood glucose in the steady-state concentrations, with additional release to cover the post-prandial glucose excursions. Hence in insulin-deficient type 2 diabetic patients, basal insulin supplemented with multiple pre-prandial injections of regular human insulin or short-acting insulin analogues, or used alone or with oral anti-diabetic drugs is necessary for intensive glucose control. Neutral Protamine Hagedorn (NPH or isophane) insulin is the most commonly used intermediate-acting insulin, administered either once or twice daily, alone or in combination with fast-acting pre-meal insulin or oral anti-diabetic drugs. Other less commonly used formulations include lente and ultralente. These insulin formulations have a tendency to aggregate into dimmers and hexamers under physiological pH and they can only be absorbed in its monomeric form following subcutaneous injection. There is considerable inter-individual variation in its dissociation and hence its absorption leading to variable day-to-day glucose-lowering effects. Furthermore, there is a significant peak of action that occurs 4-8 hours following subcutaneous NPH injection which increases the risk of nocturnal hypoglycaemia with evening administration. The subsequent decline in insulin levels may cause early morning fasting hyperglycaemia. Another drawback is the lack of 24-hour duration in a single daily injection dose.

Although the duration of ultralente is much longer, the activity is too variable to provide reliable basal insulin cover and it could accumulate increasing the risk of hypoglycaemia.

Peakless action of insulin glargine

Insulin glargine is a new long-acting human insulin analogue that is designed to overcome the above deficiencies of conventional intermediate and long-acting insulin formulations. Its structural modification confers a relatively constant concentration profile (without peaks and troughs), more physiological and a prolonged duration of action (24 hours). Pharmacokinetic studies showed that its effect is apparent within 2 hours following subcutaneous injection with a flat profile similar to that of continuous subcutaneous insulin infusion. Several clinical trials in type 2 diabetes showed that once-daily insulin glargine is at least as effective as NPH insulin in glycaemic control with lower incidence of hypoglycaemia and less weight gain. Insulin glargine has also been shown to improve vascular function in the human forearm and this may translate into an important difference in clinical outcomes.

Insulin glargine in type 2 diabetes: clinical application

As with initiation of any insulin regime, it involves a multi-faceted approach including patient education with self blood glucose monitoring, injection techniques, dietary compliance, life-style modification and management of hypoglycaemia. In insulin-naive patients, insulin glargine can be initiated at a dose of 10 units as a starting point administered subcutaneously either in the morning or evening. Patients should be taught dose titration using fasting blood glucose readings (aim to keep below 7.0 mmol/L) with gradual increase of insulin dosage at no more than 2 units each time. Insulin-sensitiser such as metformin or thiazolidinediones, or both may be used in conjunction in type 2 diabetic patients with a degree of insulin resistance to spare the amount of total insulin required in order to minimise weight gain. In patients previously treated with NPH insulin once or twice daily injection, a 25-30% reduction in total basal insulin dose is recommended when switched to insulin glargine. There are no published data regarding the optimal timing of insulin glargine injection but it appears that when added
to glimepiride, morning administration is more efficacious in glycaemic control when compared to bedtime insulin glargine and bedtime NPH insulin treatment group over a 24-week period in overweight type 2 diabetic patients.

**Practical experience with insulin glargine**

The introduction of insulin glargine has resulted in marked improvement in glycaemic control and quality of life in many type 2 diabetic patients with β-cell failure in our Diabetes Centre. We use two cases to illustrate the clinical application of insulin glargine:

**Case 1**

A 48-year old male accountant was diagnosed to have type 2 diabetes 2 years ago. He has been treated with diet all along. He presented with a short history of polydipsia and weight loss with a HbA1c of 13.0%. His body mass index was 20.7 kg/m². His HDL-cholesterol was high at 4.7 mmol/L and he had diabetic nephropathy (serum creatinine 108 umol/L with raised urine albumin creatinine ratio 5.63 mg/mmol). He was started on gliclazide, rosiglitazone and atorvastatin. Despite gradual increase of dosage, there was no significant improvement to his glycaemic control. Multiple insulin injection was started using Humulog three times daily pre-meal and glargine at night. After dosage adjustment, her glycaemic control was stabilised at HbA1c of 12.1% to 7.7% over a period of 3 months without any hypoglycaemia.

**Conclusions**

These two cases illustrate that appropriate use of insulin glargine to provide basal insulin cover resulted in marked glycaemic control without any problems of hypoglycaemia. The clinical application is simple and can be combined with insulin sensitisers such as metformin or thiazolidinediones. Regular self blood glucose monitoring, diabetes education and dietary advice remain important adjuncts in the management of diabetes, especially at initiation of insulin therapy.

**References**