Good Glycemic Control With Flexibility in Timing of Basal Insulin Supply

A 24-week comparison of insulin glargine given once daily in the morning or at bedtime in combination with morning glimepiride

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The early initiation of insulin therapy to achieve good metabolic control is being increasingly considered in type 2 diabetes (1), but barriers, including fear of hypoglycemia, need to be overcome to achieve target glycemic control (2).

Insulin glargine (glargine; Lantus) is a once-daily, basal human insulin analog. The 24-h duration and flat time-action profile of glargine (3) should give flexibility to patients in terms of the injection time despite targeting fasting blood glucose (FBG) close to normal: administration should be possible at any time of day provided it is at the same time each day. Previously, we have demonstrated similar levels of nocturnal hypoglycemia but better glycemic control with morning versus bedtime glargine plus three milligrams glimepiride (4).

RESEARCH DESIGN AND METHODS

The study objective was to compare the frequency of nocturnal hypoglycemia following morning or bedtime administration of glargine plus glimepiride. In a multinational, open-label, randomized study, 624 patients with type 2 diabetes poorly controlled on oral agents received morning or bedtime glargine plus morning glimepiride (2, 3, or 4 mg) for 24 weeks titrated to target FBG ≤100 mg/dl. Patient demographics and baseline characteristics were similar across the two treatment arms (aged 62.1 vs. 61.5 years, BMI 28.2 vs. 28.7 kg/m^2, and diabetes duration 9.5 vs. 10.3 years). The primary outcome, incidence of nocturnal hypoglycemia (hypoglycemia while the patient was asleep, after the evening injection and before rising), was compared using one-sided 95% CIs.

RESULTS

The frequency of nocturnal hypoglycemia was equivalent between the groups, with morning glargine noninferior to bedtime (13.0 vs. 14.9%, 95% CI −100 to 2.84%). Most patients who experienced nocturnal hypoglycemia had only one episode (51.3 vs. 54.8%).

At end point, clinically meaningful reductions in HbA_{1c} were observed in both groups: −1.7 ± 1.2%, from 8.8 ± 1.0 to 7.2 ± 1.1% (morning) and −1.6 ± 1.2%, from 8.8 ± 1.0 to 7.2 ± 1.1% (bedtime). A reduction in FBG also occurred: −76.55 ± 50.76 (morning) vs. −80.69 ± 49.41 mg/dl (bedtime) (P = 0.08), with no significant differences in hypoglycemia. The proportion of patients with HbA_{1c} ≤7.0% was comparable for the two treatment groups (P = 0.66), with 48% (n = 149) and 47% (n = 143) of patients achieving HbA_{1c} ≤ 7.0% at end point in the morning and bedtime groups, respectively. Baseline to end point decreases in nocturnal and mean daily blood glucose were similar in both groups (nocturnal blood glucose: −68.64 ± 58.53 vs. −70.10 ± 56.72 mg/dl, P = 0.52; mean daily blood glucose: −73.42 ± 56.55 vs. −68.35 ± 54.45 mg/dl, P = 0.13; all morning versus bedtime). Mean daily insulin dose at end point was comparable between the groups (34.7 ± 17.4 vs. 32.4 ± 17.0 IU, P = 0.15).

Treatment-emergent adverse events were observed in 308 patients, with no clinically relevant between-treatment differences. Possible treatment-related treatment-emergent adverse events occurred in 3.5% of patients (morning: 2.9%; bedtime: 4.1%); 8.0% experienced severe treatment-emergent adverse events (morning: 8.8%; bedtime: 7.3%).

CONCLUSIONS

In conclusion, glargine, due to its 24-h action and flat profile, is an appropriate and flexible add-on therapy to start insulin treatment in patients with type 2 diabetes. Flexible dosing with simple glimepiride/glargine regimens achieved significant and practically meaningful improvements in glycemic control, regardless of administration time and without differences in hypoglycemia. This flexibility should facilitate initiation of and adherence to insulin therapy and thus lead to improvements in glycemic control.

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Abbreviations: FBG, fasting blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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References

1. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
2. Korytkowski M: When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 26 (Suppl. 3): S18–S24, 2002
3. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T: Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 23:644–649, 2000
4. Fritsche A, Schweitzer MA, Haring HU: Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 138:952–959, 2003