Study Overview

Objective. To compare the safety and efficacy of 3 adjusted-dose insulin regimens (ie, morning insulin glargine, bedtime insulin glargine, or bedtime neutral protamine Hagedorn [NPH] insulin) in combination with the oral sulphonylurea glimepiride.

Design. Nonblinded, randomized controlled trial.

Setting and participants. 695 patients with type 2 diabetes previously treated with oral antidiabetic agents were recruited from 111 clinical centers in 13 European countries. All patients were younger than 75 years of age, had a body mass index less than 35 kg/m², had fasting blood glucose levels of 120 mg/dL or greater, and hemoglobin A1c (HbA1c) measurements between 7.5% and 10.5%. Patients who were pregnant, breast-feeding, had prior treatment with insulin in the past 3 months, or had somatic or mental diseases were excluded.

Intervention. Patients were randomized to receive adjusted-dose morning insulin glargine, bedtime insulin glargine, or bedtime NPH insulin. All patients received glimepiride (3 mg orally in the morning starting 4 weeks before commencement of insulin treatment). Insulin dosages were increased every week for the first 4 weeks, then every other week for the remainder of the 24-week study. If hypoglycemia did not occur and at least one of the last 2 fasting glucose measurements was greater than 100, 120, 140, or 160 mg/dL, the daily insulin dose was increased by 2, 4, 6, or 8 units, respectively.

Main outcome measures. Primary outcomes were the change in HbA1c from baseline and the frequency of patient hypoglycemic episodes during the study period. Secondary endpoints included type of hypoglycemic episode, blood glucose levels, and weight gain.

Main results. HbA1c declined more in the morning insulin glargine group (–1.24% [90% confidence interval {CI}, –1.10 to –1.38]) than in the bedtime NPH group (–0.84% [90% CI, –0.69 to –0.98]) or in the bedtime insulin glargine group (–0.96% [90% CI, –0.81 to –1.10]). HbA1c less than 7.5% was achieved by 43.4%, 32.5%, and 33.6% of patients in the morning insulin glargine, bedtime NPH, and bedtime insulin glargine groups, respectively. Fasting blood glucose was similar in all 3 groups, but mean daily blood glucose was lowest in the morning insulin glargine group. The number of hypoglycemic episodes was similar in all 3 groups, but symptomatic hypoglycemia was less common in the bedtime insulin glargine group compared with the morning insulin glargine group (43% versus 56%; P < 0.004) or the bedtime NPH group (43% versus 58%; P < 0.001). Nocturnal hypoglycemia was most common in the bedtime NPH group. Severe hypoglycemia (ie, requiring the assistance of another person) occurred in 2.2% of patients and did not differ significantly between groups. Weight gain occurred in all groups (mean, 3.5 kg), and there was a trend towards more weight gain in the insulin glargine groups (3.9-kg gain with morning dose, 3.7-kg gain with bedtime dose) as compared with the bedtime NPH group (2.9-kg gain).

Conclusion. Glimepiride combined with morning insulin glargine lowered HbA1c more than bedtime insulin glargine or bedtime NPH. Both insulin glargine regimens caused less nocturnal hypoglycemia, and bedtime insulin glargine caused the least symptomatic hypoglycemia. Weight gain may be higher with insulin glargine than with bedtime NPH.

Commentary

For patients with type 2 diabetes who cannot be controlled with lifestyle modification and oral agents alone, a confusing array of treatment choices exist. Several types of insulin are available that can be used alone, in combination with oral medications, or in combination with each other. This study is...
helpful because it compares combination therapy with bedtime NPH to the newer long-acting insulin glargine. Although originally tested for bedtime use, this study suggests that insulin glargine may provide better 24-hour glycemic control when given in the morning, and morning use leads to greater HbA1c reductions than bedtime NPH.

Before reaching the conclusion that morning insulin glargine is the best-choice insulin to add for combination with oral therapy, there are several issues to consider. This study was not blinded, and the moderate differences in outcomes observed could have been introduced by this lack of blinding. Also, the authors acknowledge that the pharmaceutical company that funded the study also was involved with the study design, data collection and analysis, and manuscript review. The impact that the industry sponsor’s involvement had, if any, on the study’s findings cannot be readily determined. Third, the trend towards greater weight gain seen with insulin glargine is disturbing, and this difference may have achieved statistical significance with more prolonged use. Lastly, only 1 oral agent was used. Further work should explore the optimal insulin regimen to use with other oral agents (ie, metformin).

This study makes clear that even with frequent titration of the daily insulin dose, only a minority of patients whose diabetes cannot be controlled with oral agents will achieve HbA1c less than 7.5% with the addition of a once-daily injection of long-acting insulin, and the majority of patients treated aggressively this way will have some hypoglycemia. Oral agents combined with once-daily insulin may result in tight control for some, but many patients are likely to need more complicated treatment regimens to minimize their risk of diabetic complications.

**Applications for Clinical Practice**

Morning use of combined adjusted-dose insulin glargine with glimepiride may be more effective at lowering HbA1c than combination therapy with glimepiride and bedtime insulin glargine or NPH. Further studies are needed to confirm this finding. Hypoglycemia is a limiting factor for all of these regimens, and many adults with type 2 diabetes who require insulin will not be able to achieve strict glucose control with a once-daily sulphonylurea and a single insulin injection.

—Review by Stephen D. Persell, MD, MPH

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