A split regimen of regular insulin at dinner and NPH insulin at bedtime reduced nocturnal hypoglycemia in type 1 diabetes

Fanelli CG, Pampanelli S, Porcellati F, et al. **Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial.** Ann Intern Med. 2002 Apr 2;136:504-14.

QUESTION

In patients with type 1 diabetes mellitus receiving intensive treatment with injections of regular insulin before meals, is the administration of regular insulin with the evening meal and neutral protamine Hagedorn (NPH) insulin at bedtime (split regimen) more effective than administering both with the evening meal (mixed regimen) for reducing nocturnal hypoglycemia?

DESIGN

8-month randomized {allocation concealed*}†, unblinded,* crossover trial.

SETTING

An outpatient diabetes clinic at a university hospital in Perugia, Italy.

PATIENTS

22 patients (mean age 29 y, 55% men) who had type 1 diabetes; were receiving long-term intensive insulin treatment; had no retinopathy, neuropathy, nephropathy, or hypertension; and were taking no medications other than insulin. Patients were excluded if they had hypoglycemia unawareness (absence of symptoms and a blood glucose level of 2.5 to 2.8 mmol/L) or episodes of hypoglycemia requiring assistance in the previous year. Follow-up was complete.

INTERVENTION

For a 1-month run-in period, patients used the split regimen and were then allocated to continue with the split regimen or to begin the mixed regimen for 4 months, after which they were switched to the other treatment for another 4 months. Insulin was administered to achieve fasting blood glucose values of 5.0 to 6.7 mmol/L before meals and at bedtime.

MAIN OUTCOME MEASURES

Nocturnal hypoglycemia, and fasting-blood glucose and hemoglobin A_{1c} levels. Patient data from the last month of each treatment period were used for the analysis.

MAIN RESULTS

When receiving the split regimen, patients had fewer episodes of hypoglycemia at 3:00 a.m., a mean of 2.8 (95% CI 1.9 to 3.7) fewer episodes of hypoglycemia, and lower fasting blood glucose and HbA_{1c} levels than when they received the mixed regimen (Table).

CONCLUSION

In patients with type 1 diabetes mellitus receiving intensive treatment, administration of regular insulin before each meal and neutral protamine Hagedorn (NPH) insulin at bedtime reduced nocturnal hypoglycemia and improved control of blood glucose levels more than mixing the evening dose of regular insulin with NPH and administering this mix with the evening meal.

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*See Glossary.

†Information provided by author.

Split vs mixed evening insulin regimen for type 1 diabetes at 8 months‡

Outcomes	Split	Mixed	*P* value or mean difference (95% CI)
Episodes of hypoglycemia at 3:00 a.m. per patient-d	0.10	0.28	0.18 (0.07 to 0.27)
Fasting blood glucose level (mmol/L)	7.6	8.9	0.030
Hemoglobin A_{1c} level (%)	7.0	7.5	0.5 (0.18 to 0.81)

‡Values are means from the last month of each treatment period. All comparisons favor the split-insulin regimen.

COMMENTARY

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Near-normal glycemia (achieved by using multiple daily insulin injections [MDI] or an insulin pump) decreases retinopathy in type 1 diabetic patients with no or early retinopathy (1) but increases the risk for hypoglycemia (mostly nocturnal) by at least 3-fold (2).

Because hypoglycemia adversely affects quality of life and glycemic control, clinicians and patients value randomized trials of insulin regimens that reduce nocturnal hypoglycemia. The study by Fanelli and colleagues showed that administration of NPH insulin at bedtime rather than with the evening meal decreased the risk for nocturnal hypoglycemia by 60%.

The investigators were not blind to allocation, an issue that would require an innovative design. The applicability of the study findings is limited by the otherwise-understandable exclusion of patients with hypoglycemic unawareness, a group particularly vulnerable to hypoglycemia.

Other investigators have successfully decreased nocturnal hypoglycemia by replacing human insulin in MDI regimens with insulin analogues (insulin lispro or aspart and glargine insulin, which cannot be mixed) (3–5). Further research to make safer and more convenient MDI regimens is eagerly awaited, including comparisons of insulin glargine with ultralente insulin and inhaled insulin as bolus insulin.

References

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