

Starting Insulin Therapy in Type 2 Diabetic Patients

Does it really matter how?

Type 2 diabetic patients failing oral antidiabetes medications need insulin. If used appropriately and with patient cooperation, almost all patients can be well controlled. There is no agreed upon optimal mode of initiating insulin in this situation. In recent years, adding NPH insulin at bedtime (1–3) or 70/30 premixed insulin at suppertime (4) to the oral medications have been studied. Adding NPH insulin at bedtime has yielded similar improvements in control as two or more injections of insulin for 3 (1), 6 (2), or 12 (3) months. Recently, several studies have compared the peakless insulin, glargine, with bedtime NPH insulin and showed similar levels of control but less nocturnal hypoglycemia (5–7).

Two reports in this issue of *Diabetes Care* pertain to this matter. In the first, Janka et al. (8) compared adding a morning injection of glargine insulin to type 2 diabetic patients failing oral medications with discontinuing the pills and starting premixed 70% NPH insulin/30% regular insulin twice a day. The patients receiving glargine insulin during the 24-week study were also taking 3 or 4 mg of glimepiride and 850 mg or more of metformin. A weekly forced-titration algorithm was used to achieve a target fasting glucose concentration of ≤ 100 mg/dl in both groups and ≤ 100 mg/dl before supper in the patients taking premixed insulin. Patients in the glargine group had a statistically greater fall in A1c levels (-1.6 vs. -1.3%) and less hypoglycemia, and more reached an A1c level of $\leq 7.0\%$ without confirmed nocturnal hypoglycemia (46 vs. 29%) than patients receiving premixed insulin.

In the second report by Raskin et al. (9), type 2 diabetic patients failing oral medications had their sulfonylurea agents and α -glucosidase inhibitors discontinued and their metformin dose optimized to 1,550–2,550 mg, and glitazone treatment was continued if patients were taking one during a 4-week run-in period.

They were randomized to receive either glargine insulin at bedtime or premixed 70% NPH insulin/30% aspart insulin twice a day for 24 weeks. Insulin doses were titrated every week for the first half of the study and every 2 weeks for the second half to achieve target fasting plasma glucose concentrations of 80–110 mg/dl in both groups and the same target before supper in patients taking the premixed insulin. In contrast to the first study (8), patients receiving premixed insulin had a significantly greater fall in A1c levels (-2.8 vs. -2.4%), and more of them reached an A1c level of $\leq 7.0\%$ (66 vs. 40%) than those receiving glargine insulin. As might be expected and similar to the first study, hypoglycemia was more common in patients receiving two injections of premixed insulin per day.

What might account for the different outcomes of the two studies? Since aspart is an analog insulin with a more rapid onset of action than regular insulin, postprandial glycemia might have been better controlled with this premixed insulin because it is doubtful that many patients using regular insulin routinely injected 30 min before eating. As intuitively expected, the more poorly controlled the patient is, the more the fasting glucose concentration contributes to overall hyperglycemia, whereas in better-controlled patients, postprandial glycemia plays a more major role. For instance, in patients with A1c levels $< 7.3\%$, postprandial glycemia accounts for $\sim 70\%$ of overall glycemia and fasting glucose concentrations account for the remaining 30% (10). Conversely, in patients with A1c levels $> 10.2\%$, the percentages are reversed. Raskin et al.'s data (9), however, argue against this postprandial hypothesis. There was no significant difference in the decrease of A1c levels in patients whose baseline values were $< 8.5\%$ (-1.4% in both groups). The difference in patients with baseline values $\geq 8.5\%$ (-3.1 vs.

-2.6%) accounted for the difference between the two groups.

Another possible explanation for the difference in the outcomes of the two studies is that no oral medications were given to the group receiving premixed insulin in the study (8) that showed a daily injection of glargine insulin plus pills was more efficacious. This seems doubtful since near euglycemia can almost always be achieved if enough insulin is given appropriately to cooperative patients (11,12). (These subjects are likely to be cooperative since they volunteered for a clinical trial.) In the study showing a slight advantage in the patients receiving premixed insulin, no sulfonylurea agents were used (9). An insulin secretagogue might have been more important in patients receiving glargine insulin because the amount of exogenous insulin provided was less than in those in the premixed insulin group.

However, in the final analysis, regardless of possible reasons for the small, but statistically significant, differences in A1c changes between patients receiving two injections of premixed insulin and those taking one injection of glargine insulin in the two studies (8,9), these small differences will not affect subsequent clinical outcomes very much, if at all. To answer the question posed in the title, it probably does not really matter what regimen one initially chooses to start insulin. The key factor is to continue to intensify the approach until targets are achieved and then to maintain them. A personal preference that minimizes interruption of the patient's lifestyle is to use up to a combination of three oral medications (13) before embarking on insulin therapy if they fail. Our third drug is a glitazone, which is prescribed at a maximal dose so that we will know in 4 months whether insulin is required (rather than stretching out the period of time that patients might remain uncontrolled on submaximal doses for up to a year). During that period, diet and

exercise are stressed to give the patient the best chance of avoiding insulin and to counter the expected weight gain with the insulin sensitizer.

Our initial regimen is bedtime NPH insulin with maximal (tolerated) doses of metformin and a sulfonylurea agent. (Our county medical care system only allows glargine insulin to be used in type 1 diabetic patients on a basal/bolus regimen.) However, if the dose of bedtime NPH insulin is gradually increased and patients ingest a bedtime snack, there has been little overnight hypoglycemia. This approach minimizes the difficulties that patients face on more intensive insulin regimens, e.g., self-monitoring more than once a day, a less flexible schedule of eating and exercise, more weight gain, and hypoglycemia. However, if that regimen fails to achieve or maintain near euglycemia, a mixed/split or, less often, a basal/bolus insulin regimen is introduced. Since near euglycemia is often not achieved with premixed insulins because the individual components cannot be adjusted separately, only those few patients who cannot be taught to mix insulins are given premixed preparations. Obese patients are kept on metformin, and the sulfonylurea agent is discontinued. If the patient's insulin secretion is unable to maintain near euglycemia while the patient is on the bedtime insulin/daytime oral antidiabetes medications, it seems doubtful that a sulfonylurea agent will be of much help on a multiple insulin injection regimen.

In conclusion, we need to keep our (and the patient's) eye on the brass ring, i.e., near euglycemia. It does not matter how we get there as long as we do. However, achieving it with the least disruptions to the patients' lifestyles (as well

as our office schedules) would seem preferable.

MAYER B. DAVIDSON, MD

From the Clinical Trials Unit, King-Drew Medical Center, Charles R. Drew University, Los Angeles, California.

Address correspondence to Mayer B. Davidson, MD, Clinical Trials Unit, Charles R. Drew University, 1731 East 120th St., Los Angeles, CA 90059. E-mail: madavids@cdrewu.edu.

© 2005 by the American Diabetes Association.

References

1. Yki-Jarvinen H, Kaupila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Ryysy L, Salo S, Seppala R, Tulokas T, Viikari J, Karjalainen J, Taskinen M-R: Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 327:1426–1433, 1992
2. Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, Menheere PP, Nieuwenhuijzen Kruseman AC: Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care* 19:1326–1332, 1996
3. Yki-Jarvinen H, Ryysy L, Kaupila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Salo S, Seppala P, Tulokas T, Viikari J, Taskinen M-R: Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 82:4037–4043, 1997
4. Riddle MC, Schneider K, the Glimepiride Combination Group: Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. *Diabetes Care* 21:1052–1057, 1998
5. Yki-Jarvinen H, Dressler A, Ziemer M, the HOE 901/3002 Study Group: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23:1130–1136, 2000
6. Rosenstock J, Schwartz SS, Clark CM, Park GD, Donley DW, Edwards MB: Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* 24:631–636, 2001
7. Riddle MC, Rosenstock J, Gerich J, the Insulin Glargine 4002 Study Investigators: The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetes patients. *Diabetes Care* 26:3080–3086, 2003
8. Janka HU, Plewe G, Riddle MC, Klieber-Frisch C, Schweitzer MA, Yki-Jarvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 28:254–259, 2005
9. Raskin P, Allen E, Hollander P, Gabbay RA, Hu P, Bode B, Garber A, the INITIATE Study Group: Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28:260–265, 2005
10. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA_{1c}. *Diabetes Care* 26:881–885, 2003
11. Andrews WJ, Vasquez B, Nagulesparan M, Klimes I, Foley J, Unger R, Reaven GM: Insulin therapy in obese, non-insulin-dependent diabetes induces improvements in insulin action and secretion that are maintained for two weeks after insulin withdrawal. *Diabetes* 33:634–642, 1984
12. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS: Intensive conventional therapy for type II diabetes: metabolic effects during a 6-month outpatient trial. *Diabetes Care* 16:21–31, 1993
13. Roy R, Navar M, Palemeno G, Davidson MB: Real world effectiveness of rosiglitazone added to maximal (tolerated) doses of metformin and a sulfonylurea agent. *Diabetes Care* 27:1741–1742, 2004