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 ≤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 ≤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 ~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 ≥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.

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