

A Patient With Type 2 Diabetes Uncontrolled on Oral Agents: The Evidence and Rationale for Basal Insulin

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Case Presentation: Type 2 Diabetes Uncontrolled on Oral Agents

William, a 51-year-old man, has had diabetes for the past 8 years but did not have regular medical care until 2 years ago when his glycated hemoglobin (A1c) level was found to be 11.1%. He was treated with metformin 1000 mg twice daily; glimepiride 4 mg daily and pioglitazone 45 mg daily were both added subsequently. He has diabetic nephropathy and his creatinine is 1.7 mg/dL with an estimated glomerular filtration rate of 48 mL/min/1.73m². His A1c level is currently 8.5%, and his home glucose levels average 170 mg/dL before breakfast and 140 mg/dL before dinner. What is the recommended next step for William?

Principles of Insulin Treatment

For many years there have been 2 basic approaches to glycemic treatment of type 2 diabetes with insulin: basal insulin treatment with a variety of intermediate- and long-acting insulin preparations; and bolus or prandial treatment with more rapidly acting forms of insulin administered prior to meals. A third approach has also been employed which uses combinations of intermediate- and short-acting insulin, typically in a ratio of three quarters to one quarter. The rationale for choosing one of these approaches or a combination basal-bolus regimen is fascinating and complex.

Clearly, insulin is effective in the treatment of type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), more than 4000 patients newly diagnosed with type 2 diabetes were randomly assigned to a variety of treatments, with more than 1100 receiving insulin. Although a form of basal insulin, ultralente, was given as initial treatment, patients who received > 12 units (U) daily (somewhat more if obese) were asked to measure blood glucose before meals and at bedtime. If levels exceeded 127 mg/dL, premeal regular insulin was added.^[1] A subset of approximately 300 patients in the UKPDS received sulfonylureas as initial treatment; insulin was added if fasting glucose levels exceeded 108 mg/dL. More than half of the patients required the addition of insulin over the 6-year observation period. They showed a greater degree of improvement in glycemic control than patients who received insulin alone, without an increase in hypoglycemia frequency or in weight,^[2] exemplifying the BIDS (bedtime insulin, daytime sulfonylurea) approach that had become popular in the preceding decade.^[3] Insulin-based treatment approaches were shown to confer more durable glycemic control than sulfonylureas over a 9-year follow-up in the UKPDS.^[4] Although in shorter-term studies the combination of a sulfonylurea, pioglitazone, and metformin had glycemic efficacy similar to that of combination insulin-metformin, the insulin-based approach was associated with less weight gain and less hypoglycemia,^[5] further validating the use of insulin in patients with type 2 diabetes.

Most of these studies used a form of basal-bolus treatment, raising the question of which component is more effective in controlling glycemia. Administering insulin intravenously at the onset of a meal to mimic the normal insulin secretory response to meals essentially normalizes the postprandial increment in glucose seen in diabetic persons.^[6] A number of studies have used treat-to-target approaches with a moderate starting dose of intermediate- or long-acting insulin, typically 6-10 U, and with dose increments of 2-8 U as often as twice weekly to attain the desired fasting

glucose level after administration of NPH (neutral protamine Hagedorn), glargine, or detemir insulins at bedtime.^[7-9] These studies showed comparable reduction in A1c levels with the 3 studied insulin preparations, although glargine and detemir have been associated with approximately one third fewer episodes of hypoglycemia.

William: Recommendation for Next Steps

Because of his renal insufficiency, William's metformin was tapered off and basal insulin was added at bedtime, with the dose gradually increased to achieve a fasting glucose of 100 mg/dL. We will consider whether a basal-insulin-only approach is the correct way to manage patients who require addition of insulin.

Safety and Efficacy of Premeal Rapid-Acting Insulin Analogs

Several studies have directly compared long-acting insulin preparations with premeal rapid-acting analogs. One early study in sulfonylurea-treated patients compared insulin lispro given before each meal to NPH given at bedtime and found that although the latter approach more effectively lowered fasting glucose, it was less effective in reducing A1c.^[10] The researchers, however, did not administer NPH in a sufficiently high dose to normalize fasting glucose. An interesting study compared 1115 patients randomly assigned after myocardial infarction to insulin lispro 3 times daily or to a basal strategy of NPH insulin twice daily or insulin glargine daily, with mean follow-up of nearly 3 years. The investigators used A1c targets of < 7%, and although a specific treatment algorithm was not described for pre- and postprandial glucose in the lispro and basal insulin groups,^[11] A1c decreased from 8.3% at baseline to 7.7% and 7.8% in the prandial and basal groups, respectively.^[12] Fasting glucose was lower with basal insulin, while postmeal levels were lower with lispro. Fifty-five percent of patients in both groups experienced hypoglycemia, with a trend to more severe hypoglycemia in the lispro group (13% vs 10%). Nocturnal hypoglycemia occurred in 11% of patients in the basal insulin group, significantly more frequently than in the lispro group (6%). Weight gain was 11 lb with lispro, significantly greater than the 6.6-lb weight gain with basal insulin. There was no difference in cardiovascular event rates.

Because none of these studies used algorithm-based approaches to ensure that specific glycemic goals were attained, it is useful to review studies in which the protocols for insulin dose adjustment were precisely described (Tables 1-3).

The 4-T Study

The 4-T (Treating to Target in Type 2 Diabetes) study randomly assigned 239 persons receiving metformin and a sulfonylurea to insulin aspart given 3 times daily before meals, 235 to biphasic aspart 70/30 twice daily, and 234 to insulin detemir. The titration algorithm is shown in Table 1.^[13]

Table 1. Titration Regimen Employed in the 4-T Study

<ul style="list-style-type: none">◆ Starting daily insulin dose: 16 U (range, 2-76 U)◆ Formula based on fasting glucose, height, weight◆ Titration based on 3 profiles prior to each contact:<ul style="list-style-type: none">✓ Reduce dose 10% or 4 U (the greater) if grade 3 hypoglycemia or mean glucose < 56 mg/dL, otherwise by 5% or 2 U (the greater)✓ Increase dose 10% or 4 U (the greater) if mean is > 72 mg/dL above target, otherwise by 5% or 2 U (the greater)◆ Target glucose: 72-99 mg/dL premeal (just breakfast and dinner in detemir and biphasic groups), 90-126 mg/dL 2 hours postmeal and bedtime (aspart 3 times daily group only)
<p>Twice-Daily Biphasic Insulin Dose Titration</p> <p>Increase breakfast insulin dose (when no hypoglycemia):</p> <ul style="list-style-type: none">◆ If more than 1 of 3 of pre-evening meal glucose readings remain high

Increase pre-evening meal insulin dose (when no hypoglycemia):

- ◆ If more than 1 of 3 of pre-breakfast meal glucose readings remain high

Decrease insulin doses in the presence of:

- ◆ Any grade 2 or 3 hypoglycemic episodes at relevant timepoints
- ◆ Mean glucose readings < 70 mg/dL at relevant timepoints

Thrice-Daily Prandial Insulin Dose Titration

Increase breakfast insulin dose (when no hypoglycemia):

- ◆ If more than 1 of 3 of 2-hour post-breakfast or pre-lunch glucose readings remain high

Increase lunch insulin dose (when no hypoglycemia):

- ◆ If more than 1 of 3 of 2-hour post-lunch or pre-evening meal glucose readings remain high

Increase evening meal insulin dose (when no hypoglycemia):

- ◆ If more than 1 of 3 of 2-hour post-evening meal, pre-bedtime, and pre-breakfast glucose readings remain high

Decrease insulin dose in the presence of:

- ◆ Any grade 2 or 3 hypoglycemic episodes at relevant timepoints
- ◆ Mean glucose readings < 70 mg/dL at relevant timepoints

Once-Daily Basal Insulin Dose Titration

Increase pre-bedtime insulin dose (when no hypoglycemia):

- ◆ If more than 1 of 3 of pre-breakfast meal glucose readings remain high

Add a pre-breakfast insulin injection:

- ◆ If glucose readings are at target before breakfast but not before the evening meal and nocturnal hypoglycemia limits further pre-bedtime insulin dose increases

Decrease insulin doses in the presence of:

- ◆ Any grade 2 or 3 hypoglycemic episodes at relevant timepoints
- ◆ Mean glucose readings < 70 mg/dL at relevant timepoints

Protocol from Holman RR, et al; 4-T Study Group.^[13]

At 1 year, A1c fell from a baseline level of 8.5% to 7.2%, 7.3%, and 7.6% in the prandial, biphasic, and basal groups, respectively; the decrease with detemir was significantly less than that in the groups with rapid-acting insulin, despite this group having (as would be expected) the greatest fall in fasting glucose. It is not altogether clear that this implies superiority of prandial insulin treatment. Severe hypoglycemia rates were 8%, 3.9%, and 0%, and weight increased by 12.6, 10.4, and 4.2 lb, respectively. The study was made particularly clinically relevant by allowing patients to intensify to a basal-bolus regimen over 3-year follow-up. Using this approach, at the end of the study, A1c levels averaged 6.8%, 7.1%, and 6.9% in the 3 groups ($P = .28$), and weight gain and hypoglycemia rates remained greatest in the prandial group and lowest in the group initially assigned to basal insulin.^[14] The median numbers of hypoglycemic events were 6, 3, and 2 per patient per year in the prandial, biphasic, and basal groups over the entire 3-year study period, with death from cardiovascular disease in 9, 4, and 1 of the patients in the respective 3 groups ($P = .002$). This is a significant difference, leading one to wonder whether there might be a relationship between hypoglycemia and adverse outcome. Although such an analysis has not yet been carried out in the 4-T study, in both the ADVANCE^[15] (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) and ACCORD^[16] (Action to Control Cardiovascular Risk in Diabetes) studies a significant association was reported between hypoglycemia and mortality.

The APOLLO Study

APOLLO (A Parallel design comparing an Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetes patients failing Oral treatment) was another randomized controlled trial of type 2 diabetic persons inadequately controlled on oral agents and which used a titration algorithm. The study compared 205 patients started on insulin glargine once daily (with dose titration based on fasting glucose) with 210 patients given insulin lispro 3 times daily over a 44-week period (with titration based both on pre- and postprandial glucose levels). The titration algorithm is shown in Table 2.^[17]

Table 2. Titration Regimen Employed in the APOLLO Study

Insulin glargine: starting dose 10 U/day

- ◆ Insulin dose-titration algorithm based on self-monitored fasting blood glucose for 2 consecutive days with no severe hypoglycemia:
 - ✓ > 160 mg/dL: + 8 U/day
 - ✓ > 140-160 mg/dL: + 4 U/day
 - ✓ > 100-120 mg/dL: + 2 U/day
 - ✓ ≤ 100 mg/dL: no further titration

Insulin lispro: starting dose 4 U prior to each meal. Further adjust insulin dose if A1c > 7%

- ◆ Insulin dose-titration algorithm for preprandial blood glucose:
 - ✓ > 200 mg/dL: + 3 U before prior main meal (eg, breakfast, lunch and the main evening meal)
 - ✓ > 150- ≤ 200 mg/dL: + 2 U before prior main meal
 - ✓ > 100- ≤ 150 mg/dL: + 1 U before prior main meal
 - ✓ ≤ 100 mg/dL: no further titration
- ◆ Insulin dose-titration algorithm for postprandial blood glucose:
 - ✓ > 185 mg/dL: + 2 U before main meal
 - ✓ > 135-185 mg/dL: + 1 U before main meal
 - ✓ ≤ 135 mg/dL: no further titration

Protocol from Bretzel RG, et al.^[17]

A1c fell from 8.7% to 7.0% in the glargine group vs to 6.8% in the lispro group, with lower fasting glucose in the glargine group but higher levels in the glargine group after breakfast, lunch, and dinner. However, 136 patients in the glargine group vs 189 in the lispro group experienced hypoglycemia, with a total of 876 vs 4125 hypoglycemic events, respectively. Weight gain was similar at 6.6 vs 7.7 lb.

South Danish Diabetes Study

The South Danish Diabetes Study compared 183 patients receiving NPH with 188 patients receiving preprandial insulin aspart. The titration algorithm is shown in Table 3.^[18]

Table 3. Titration Regimen Employed in the South Danish Diabetes Study

NPH given at bedtime: starting dose 12 U

- ◆ Insulin dose-titration algorithm based on fasting blood glucose for 3 consecutive days with no "unacceptable hypoglycemic episodes":
 - ✓ > 216 mg/dL: + 6 U/day
 - ✓ > 144 mg/dL: + 4 U/day
 - ✓ > 101 mg/dL: + 2 U/day
 - ✓ ≤ 100 mg/dL and A1c < 6.5%: no further titration

Insulin aspart: starting dose 4 U before each meal

- ◆ Insulin dose-titration algorithm based on self-monitored 90-minute postprandial blood glucose for 3 consecutive days with no "limiting hypoglycemic episodes":
 - ✓ > 198 mg/dL: + 3 U before that meal (eg, breakfast, lunch, or main evening meal)
 - ✓ > 162 mg/dL: + 2 U before that meal
 - ✓ > 135 mg/dL: + 1 U before main meal
 - ✓ < 135 mg/dL and A1c < 6.5%: no further titration

Protocol from Gram J, et al.^[18]

A1c reductions were 0.4% greater in the insulin aspart group, with fasting glucose lower in the NPH group and daytime glucose lower in the insulin aspart group. The preprandial bolus regimen increased the frequency of hypoglycemia and caused greater weight gain. The aspart and NPH groups experienced 861 and 723 adverse events, respectively ($P < .003$). There were nonsignificant increases in the numbers of withdrawals with insulin aspart (36 vs 26), including 4 vs

0 deaths. The study also randomly assigned patients to no oral hypoglycemic agents, metformin alone, rosiglitazone alone, and both metformin and rosiglitazone; only with both insulin sensitizers did the majority of patients in both the NPH and aspart groups achieve A1c levels $\leq 7\%$.

Expert Commentary

We may conclude from these studies that, on balance, initial treatment with basal insulin appears to be advantageous in establishing optimal fasting glucose levels, while an effort to control diabetes with initial prandial insulin will not be as effective. In contrast, basal insulin is less able to achieve control of daytime glucose levels, particularly after meals, although prandial bolus insulin will lead to more hypoglycemia and is associated with greater weight gain. Clinicians are tempted to consider the weight gain a consequence of low glucose causing increased food intake. Although it has long been recognized that improved glycemic control with insulin leads to weight gain,^[19] it is fascinating to realize that the direct effect of insulin is as a physiologic feedback signal to the central nervous system, leading to reduction in food intake,^[20] so that the full explanation of the weight gain remains uncertain. If the use of basal insulin is somewhat limited in its ability to control glucose levels during the day and prandial insulin is less effective at controlling fasting glucose, the inescapable conclusion is that optimal treatment of many insulin-requiring type 2 diabetic patients will require a basal-bolus regimen similar to that typically used in type 1 diabetes. The greater effort required on the part of both the patient and the healthcare team should be repaid in more balanced control of blood glucose with less likelihood of hypoglycemia and weight gain. This conclusion is strengthened by the 4-T study finding that initial basal insulin with gradual addition of prandial insulin is the optimal approach, balancing long-term glycemic control with acceptable weight gain, less hypoglycemia, and, perhaps, fewer adverse outcomes. It is noteworthy that studies using strict titration algorithms are more successful in achieving glycemic goals; such an approach should be considered in clinical treatment as well. The importance of insulin sensitization is brought out by the South Danish Diabetes Study findings of impressive benefit with combined administration of metformin, a thiazolidinedione, and either basal or preprandial bolus insulin.

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