Using New Insulin Strategies in the Outpatient Treatment of Diabetes

Clinical Applications

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As the number of patients with diabetes mellitus (DM) grows, largely due to an epidemic of obesity, the number of patients treated with insulin will also increase. Most patients with type 2 DM progressively lose β-cell function. Although earlier diagnosis will change these data, newly diagnosed patients with type 2 DM have less than 50% of normal insulin secretion at diagnosis, and less than 25% of normal insulin secretion 6 years after diagnosis (see Figure 4 in the accompanying article). This decline in β-cell function explains the initial and secondary failure of oral agents in patients with type 2 DM. Meticulous glucose control decreases long-term microvascular complication rates. In patients who have had recent myocardial infarction, aggressive insulin therapy aiming for tight glucose control is associated with reduced mortality.

These data have led the American Diabetes Association to recommend that patients aim for hemoglobin (Hb) A1C levels of less than 7%. A 1990s “Diabetes Report Card for the United States” found that only 29% of patients with DM had their HbA1C tested in the previous year. Of those patients, 18% had an HbA1C level of 9.5% or higher (poor control), only 43% had an HbA1C level of less than 7%, and the median HbA1C level was 7.5%.

The addition of bedtime injection (9 PM) intermediate- or long-acting insulin to oral agents have significantly improved glycemic control in patients with uncontrolled type 2 DM, but clinicians and patients often delay starting insulin therapy. In the past, hypoglycemia has been the main concern of physicians aiming for tight glycemic control. However, a better understanding of physiologic insulin replacement with basal and prandial insulins simplifies insulin dosing and adjustment. The truly basal insulin analogue, insulin glargine, and the rapid-acting insulin analogues, insulins lispro and aspart, have further improved physicians’ ability to match patients’ insulin needs. Since physiologic insulin replacement can improve control while causing fewer episodes of hypoglycemia, primary care clinicians should become familiar with these regimens, which are easier to use than many patients and clinicians realize. In our own clinical experience, the perceived complexity of insulin regimens, the difficulty in finding straightforward practical clinical information and resources (Box 1), and misconceptions about the cost and risks of insulin therapy are major barriers to physician and patient use of insulin. While the main purpose of complex insulin dose adjustments and supplements (see accompanying article) is to allow maximum flexibility and to improve glycemic control, a simple conceptual approach to insulin use (eg, basal-prandial) and understanding associated tools, such as carbohydrate counting, allows patients and physicians to improve diabetes care.

See also p 2254 and Patient Page.

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therapy are very unlikely to reach a target of 9% or higher who are receiving monotherapy. In general, single oral agents combination therapy lowers HbA1C by 2%. Thus, patients with an HbA1C level 10% despite increasing glyburide to 10 mg twice daily.

This case illustrates secondary failure of an oral agent. He will require insulin to achieve an HbA1C level of less than 7%. In general, single oral agents lower HbA1C levels by 1% to 2% and combination therapy lowers HbA1C by 2%. Thus, patients with an HbA1C level of 9% or higher who are receiving monotherapy are very unlikely to reach a target HbA1C level of less than 7%. Unfortunately, like many other patients, patient 1 was reluctant to take insulin. Therefore, metformin, 1000 mg twice daily, was added to his regimen and glyburide was reduced to 5 mg, twice daily. He did not follow-up until 2 years later when his HbA1C level was 11% while using this regimen.

In patients with residual insulin production, using bedtime neutral protamine Hagedorn (NPH; isophane insulin) or insulin glargine to provide basal insulin while continuing an oral agent, such as glyburide or metformin, to boost prandial glucose disposal, is an effective strategy. Limited data show that sulfonylureas (SUs) added to insulin produce mildly better glycemic control with fewer episodes of hypoglycemia than insulin alone. A major study comparing bedtime NPH plus metformin, bedtime NPH plus glyburide, glyburide plus metformin, and NPH alone in the morning and at bedtime found that bedtime NPH and metformin produced the best control, the fewest hypoglycemic episodes, and the least weight gain. When adding insulin to a regimen, bedtime basal insulin is a reasonable first step, especially for a patient who is reluctant to start insulin therapy. A sensible starting dose is 10 to 20 U of NPH, but 40 to 60 U or more is typically required (Box 2). The duration of disease for patient 1 suggests that he also may need prandial insulin to achieve optimal control.

Cost varies by drug and by dose. Oral agents, even generic, used in combination are often more expensive than insulin products. Using generic pricing, the estimated cost of the regimen for patient 1 (glyburide, 5 mg twice daily, and metformin 1000 mg twice daily) is $67 per month (www.drugstore.com, as of January 2003). For a starting regimen of insulin of 15 U/d, the cost is approximately $34 per month for NPH or approximately $54 per month for insulin glargine, including syringes and alcohol wipes. If patient 1 were to continue using glyburide or metformin, this would add $12 or $55 per month. Finally, the cost of a treatment program is strongly influenced by the frequency of capillary blood glucose (CBG) testing ($0.65 per test). Since basal insulin regimens can often be initiated and maintained based on fasting CBG levels, they can have relatively low monitoring costs.

Patient 2
A 68-year-old Filipina woman with type 2 DM and congestive heart failure has been taking 70% NPH/30% regular (70%/30%N/30%R or 70/30) insulin for 4 years. She takes 16 U every morning and 12 U every evening. Her fasting CBG levels are 120 to 150 mg/dL (6.7-8.3 mmol/L) but she develops hypoglycemia if she eats lunch late. Her predinner CBG levels are 180 to 240 mg/dL (10.0-13.3 mmol/L). She walks every afternoon to try to control her predinner glucose level. Her diet is high in rice and other complex carbohydrates. Her HbA1C level is 8.5%.

Options for insulin therapy for patient 2 include using split-mix (the pa-
tient mixes the insulin) NPH/R or Ultralente (insulin zinc extended) (UL)/R, but premeal and nocturnal hypoglycemia are common if meal timing is not precise (eg, late lunch [see Figure 2 in accompanying article]). Premixed 70% N/30% R insulin is more convenient but it has the same problems as the split-mix regimen because the tail of the regular insulin action overlaps with the peak NPH action in late morning and at night. In our clinical experience, many patients receiving twice-daily NPH insulin and prandial regular insulin, who are aiming for or who appear to have good glycemic control, have wide fluctuations of glucose levels with very high glucose levels immediately after breakfast and dinner and hypoglycemia before lunch and at night. This risk of nighttime hypoglycemia is the reason for the traditional bedtime snack. The premixed, neutral protamine lispro (insulin lispro protamine; NPL)/lispro (L) insulin analogue combination (75% NPL/25% L) is a good option for patients with high-carbohydrate diets or who experience prelunch hypoglycemia. Insulin NPL has a peak similar to that of NPH, but the shorter duration of action of insulin lispro, compared with regular insulin, means less overlap (Figure 1) and thus reduced risk of hypoglycemic episodes.13–15

Patient 2 refused basal/prandial insulin because of the additional injections required. Using twice-daily 75% NPL/25% L, at the same dose improved her HbA1C levels from 8.5% to 6.2% with a magnitude of benefit when switching from regular insulin to insulin lispro with meals, and more careful timing of injection of split-mix NPH and regular insulin (rather than premixed) might accomplish the same benefit, but many patients cannot attain and sustain that level of precision. Finally, most patients with type 2 DM need 1 U/kg or higher to obtain an HbA1C level less than 7%.16–18 This patient’s excellent control while receiving low doses of insulin is unusual, possibly reflecting her high ethnic risk of type 2 DM at a low body mass index (27 kg/m²), a relatively early switch to insulin therapy, and her vigorous walking program.

We have recently seen increasing confusion regarding insulin prescription-writing practices. Traditionally, many physicians use the abbreviations “R” for regular, “N” for NPH, or “L” for Lente (insulin zinc). However, “L” can now mean Lente, Lantus (Aventis Pharmaceuticals Inc, Bridgewater, NJ), or lispro; “N” can mean “NovoLog” (Novo Nordisk, Princeton, NJ), NPL, or NPH. Thus, we advocate writing out the insulin name in full. Furthermore, use of the abbreviation “U” for units may be misinterpreted as a zero, for example, 5 U translated to 50, if not written clearly.

**Patient 3**
A 76-year-old woman with type 2 DM takes 70% N/30% R insulin, twice daily. Despite multiple discussions and intermittent good glycemic control for several months at a time (HbA1C range, 7.2%-8.6%), her adherence is affected by her schedule. She prefers to get up after 10 AM some days and her meal schedule is very erratic, but she usu-
Insulin stacking, administering injections too close together in time, of any type of insulin results in hypoglycemia if patients already have reasonable glycemic control. As depicted in the figure, the additive effect of the insulin profile explains why patients would experience episodes of evening or nighttime hypoglycemia and fasting hyperglycemia. Arrows indicate insulin injection; NPH, neutral protamine Hagedorn (isophane insulin).

Insulin glargine is peakless with a 20- to 24-hour duration of action, and thus can be given once a day and causes fewer episodes of hypoglycemia than NPH.6 Neutral protamine Hagedorn has a 10- to 16-hour duration with a significant peak, and, as typically used, has both basal and prandial components. Although many patients may have adequate control with use of bedtime NPH, studies comparing insulin glargine to NPH show lower fasting blood glucose (FBG) levels and better postdinner control with equivalent daytime control. More important, insulin glargine causes fewer serious adverse effects, including 25% fewer episodes of hypoglycemia at night and less weight gain (1 kg less at 28 weeks).6 Lastly, one study of patients with type 1 DM showed significantly better patient treatment satisfaction, and patients perceived fewer episodes of hypoglycemia or hyperglycemia while taking insulin glargine than they did while using either single- or multiple-dose NPH insulin regimens.19

Insulin glargine is clear and therefore can be confused with other clear insulins. It must be given separately from other insulins and is best given at bedtime with dose adjustment guided by FBG measurements. When starting a basal-prandial insulin regimen, the major considerations affecting the dose are weight, current glycemic control, and degree of insulin resistance. Generally, if a patient weighed 80 kg, a sensible starting basal dose would be 8 to 16 U of NPH or glargine at bedtime (Box 2).

Persistence in adjusting insulin doses to reach target CBG levels is essential. Prandial insulins include regular insulin, insulin lispro, and insulin aspart. The latter 2 are more convenient since they can be given as a mealtime injection rather than 30 minutes prior to a meal. These insulins are called rapid-acting insulins because they begin to act in 5 to 15 minutes, peak at 30 to 90 minutes, and remain in the body for 5 hours.

Many patients with diabetes use carbohydrate counting as the primary tool to determine prandial insulin supplements using an insulin algorithm that uses their usual insulin dose, current CBG level, and expected exercise and food consumption. Although the protein and fat content of a meal are important, it is the carbohydrate content that has the greatest influence on patients’ glucose levels and insulin needs. The carbohydrate content of foods can be easily determined from food labels. A typical prandial insulin algorithm gives 1 extra unit of rapid-acting prandial insulin (lispro or aspart) per 10 to 15 g of carbohydrate. Patients with type 2 DM may need ratios of 1 U insulin for every 3 to 5 g of carbohydrate (see Web site: http://www.diabetes.org/wizdom/download//food.asp#carb%20counting).

Patients give additional insulin supplements based on the premeal CBG level (1-2 U per 50 mg/dL [2.8 mmol/L] over 150 mg/dL [8.3 mmol/L]). Thus, if the CBG level of patient 3 is 250 mg/dL (13.9 mmol/L) and she plans to eat a 60-g carbohydrate meal, she would take 2 U of insulin as a premeal supplement for 100 mg/dL (5.6 mmol/L) over 150 mg/dL (8.3 mmol/L), plus 4 U at 1 U per 15 g of carbohydrate; a total of 6 U of prandial insulin. Although carbohydrate counting adds flexibility,20 it may be too complicated for some patients. Alternatively, insulin dosing can be based on diet history using conservatively estimated percentages of carbohydrates or calories at each meal. Subsequent adjustments are based on accumulated patient experience and CBG values. Help from a diabetes educator is invaluable in training patients in self-management skills.

**Patient 4**

A 37-year-old woman with type 1 DM who takes metoclopramide for gastroparesis develops nausea, vomiting, and epigastric pain. She uses an insulin pump with insulin lispro (basal 0.9 U/h,
1 U per 10 g of carbohydrate). She reports frequent episodes of hypoglycemia and has been unable to take her oral medications. She is admitted to the hospital for an esophagogastroduodenoscopy the next day.

Long-term management of patients with type 1 DM using insulin pumps is usually best done by a specialty care team. However, continuing patients on their own pumps, for tests or short hospitalizations when they need to be fasting, is usually the easiest treatment plan. Their basal infusion is used alone when they are fasting and it is adjusted based on usual CBG monitoring. Basal needs are affected by insulin resistance from endogenous stress cortisol or medications and, typically, by decreased physical activity. Patients’ prandial insulin needs vary depending on their food intake.

**Patient 5**

A 70-year-old woman with type 2 DM presents with headache, myalgia, and sweats. Results of the evaluation show giant cell arteritis, and prednisone 60 mg/d is started. Her diabetes medications are affected by insulin resistance from endogenous stress cortisol or medications and, typically, by decreased physical activity. Patients’ prandial insulin needs vary depending on their food intake.

In persons taking corticosteroids, the primary defect is impaired disposal of glucose after meals. Corticosteroids increase gluconeogenesis, suppress insulin secretion, and decrease peripheral uptake of glucose. It is likely that in patient 5, her current postprandial CBG levels are 200 mg/dL (11.1 mmol/L) or higher. The usual goal in patients with steroid-induced or steroid-aggravated DM is to prevent glycosuria and symptoms of DM. The American Diabetes Association recommends fasting CBG levels lower than 110 mg/dL (6.1 mmol/L) and postprandial CBG levels lower than 180 mg/dL (10.0 mmol/L). Patients who already have DM should increase self-monitoring, ideally collecting baseline data 1 to 3 days before starting prednisone. Short-acting secretagogues (eg, repaglinide) or additional long-acting oral agents may have a role in treating steroid-induced DM, but the likelihood of meeting the treatment goals outlined above for the duration of this steroid treatment for patient 5 is low. It is likely that she will need to take insulin. Whether to give her both basal and prandial insulin depends on her CBG levels, although it is probable that prandial insulin alone will be sufficient since many patients with steroid-induced DM have relatively normal FBG levels. Insulin lispro or aspart are ideal agents in this case. For patients who do not have DM before beginning prednisone, periodic evaluations of postprandial CBG levels may be the most sensitive way to diagnose steroid-induced DM.22

**CONCLUSIONS**

Understanding physiologic insulin replacement and implementing new insulin strategies should allow clinicians and patients to reduce episodes of hypoglycemia and improve glycemic control. The combination of bedtime NPH or glargine and an oral agent improves glycemic control in patients with type 2 DM and is easier and less costly to implement than often assumed. Basal-prandial insulin strategies are easy to use and often improve patients’ understanding and self-management skills, and increase dosing and mealtime flexibility.

**Acknowledgment:** We thank Irl B. Hirsch, MD, for his helpful comments on the final manuscript.

**REFERENCES**


