

Physicians' Corner

Shopping for Basal Insulin on the Coffee Aisle: Lots of Choices for Lots of Tastes

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I think most clinicians would agree that there has been widespread acceptance of the use of basal insulin in the primary care community. In recent months, I have rarely encountered primary care practitioners who are uncomfortable with initiation and titration of basal insulin. Most practitioners understand and accept its utility in the diabetes treatment paradigm. When I do find confusion relating to basal insulin, I have been impressed that it relates most often to uncertainty about which product to use. There are currently 3 insulins that can be considered “basal” and several more pre-mixed products that contain basal components (**Table**). It is not unusual for this array of choices to create confusion.

My wife recently asked me to stop by the grocery store to buy coffee. She even told me the brand we use. How much more basic a task could one be assigned? Everyone knows how to buy coffee; it's a simple job, right? Well, it turned out to be anything but simple. Once I arrived at the coffee aisle, I had to decide on coffee beans or ground coffee. Then I was confronted with dark roast versus regular blend. Then came the decision regarding Colombian or other geographic regions unknown to me. Next I was faced with the can or soft-pack dilemma. I left the coffee aisle very uncertain of my success in carrying out this seemingly uncomplicated task. Then the clerk at the register asked, “Paper or plastic?” I paid the clerk, tucked the coffee under my arm, and slouched out of the store a confused and somewhat befuddled man, tired of making decisions he was ill prepared to make.

MANY CHOICES ON THE SHELF

Even though clinicians know the concept of basal insulin and seemingly are embracing it, I suspect that the array of choices and the claims of the various basal insulins leave them much as I felt in the coffee aisle. The book *Blink: The Power of Thinking Without Thinking*¹ explores the confounding effect of too many choices. Observation has taught me that preferences for basal insulin have strong geographic ties, just like the geographic affinity for coffees. In some areas, neutral protamine Hagedorn (NPH) insulin is being actively used in basal regimens. In other places, there is a strong bias toward premixed insulin products. In yet other locations, basal insulin analogues are used almost exclusively. Clearly, managed care, state Medicaid and similar plans, and institutional formularies all shape basal insulin selection throughout regions. In the absence of a clearly proven superior product, it is not unreasonable for clinicians to yield to these pressures. However, just like making good coffee, clinicians are likely to find acceptance and use of basal insulin more satisfying and reproducible if they can find a “favored brew” and develop a system for using it through repetitive practice. The real challenge is to find what insulin they are comfortable with and develop a systematic method of using it.

Considering the wide array of basal insulins, one will quickly discover that no single insulin comes to the top as “the best choice,” just as no brand of coffee is universally accepted as the best. Much has to do with issues of familiarity, brand comfort, side-effect profiles, and ease of use; but, like coffee, some properties of basal insulin are more important than others. I want my coffee to have a rich aroma, dark color, and smooth taste. These expectations shape my choice in coffee selection. Clinicians similarly need to have a full understanding of the individual properties of the basal insulin products under consideration in order to make a comfortable selection for their usual basal insulin. Some properties may pose an absolute “no-go” barrier to the clinician (eg, excessive hypoglycemia, multiple daily injections), whereas other factors may affect the decision more relatively. With this background, let us now explore the common choices for

Table. Common options for initiating insulin therapy.

Basal insulin:

- NPH insulin (at bedtime)
- Insulin detemir (once or twice daily)
- Insulin glargine (once daily)

Premixed insulin preparations:

- 70/30 NPH insulin/regular insulin
- 50/50 NPL insulin/insulin lispro
- 70/30 NPA insulin/insulin aspart
- 75/25 NPL insulin/insulin lispro

NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; NPA = neutral protamine aspart.

basal insulin and their basic properties. Keep in mind that for your patients with type 2 diabetes mellitus (DM) who have already tried 1 or 2 oral agents and have a glycosylated hemoglobin (A1C) <8.5%, 50% or more of the basic physiologic deficit is in basal insulin provision by β -cells²—so remember that you're shopping for something important!

NPH—IS THE OLDEST “THE BEST”?

NPH insulin is the oldest and least expensive of the basal insulins in common use.³ It has been around for decades, but that does not give it an undisputed claim to be “the best.” The 2 main issues with NPH are its short duration of action (12–14 hours) and its peak of action, which can pose hypoglycemic barriers.⁴ Although neither of these properties precludes NPH use as basal insulin, they certainly make insulin therapy more difficult for both the clinician and the patient. If true 24-hour coverage is desired, twice-daily dosing is dictated.

The peaking effect of insulin also adds a challenge. As tighter control is targeted, the peaking of insulin action may cause periods of hypoglycemia or drive the patient to defensively eat to avoid this consequence. Naturally, excessive eating will contribute to weight gain.

At the recent 68th Scientific Sessions of the American Diabetes Association, the results of the intensive-treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial were released and discussed.⁵ The investigators found that intensive therapy (targeting normal A1C levels) increased mortality and did not significantly decrease the incidences of major cardiovascular events. Several published editorial comments have followed, pointing out that the findings of the ACCORD trial suggest that hypoglycemia may lead to bad clinical outcomes and that excessive weight gain may do the same.^{6,7} These findings should give us pause in selecting NPH insulin as our basal choice because other products can accomplish basal supplementation with far less risk.

Inpatient variability also needs to be considered when using NPH insulin.⁸ Like poorly ground coffee that brews up strong one day and weak the next day, NPH has long been known to have day-to-day variability of action in a given patient. This may be due, in part, to the failure of patients to adequately redistribute the product before using it (ie, the “cloudiness” must be well mixed in the vial prior to use) and to absorption dynamics after injection.⁹ This inpatient variability adds one more layer of complexity and irregularity to the use of NPH as basal insulin and may actually limit its use.

HOW DIFFERENT IS PREMIXED INSULIN?

Premixed insulin products that contain some human-derived NPH and some regular insulin components or some mixture of long- and short-acting analogues (usually a 70/30 or 75/25 ratio, long- to short-acting) are fairly popular for initial basal use in the Southeastern United States, where I practice. As is obvious, these are not solely basal insulins; a basal component is part of their makeup. Several commentators have stated that there is very little clinical difference between the analogue and the human derivatives.^{2,10} Thus, one would expect these products to behave much like their basic component—an NPH-like, long-acting insulin. Therefore, what has been said above about NPH insulin will broadly apply to the premixed products. In an American Diabetes Association Webcast,² Dr. Matt Riddle noted that NPH and premixed products are fairly efficacious in lowering the A1C to ~8.0%; however, as the clinician pushes the A1C lower, inherent problems with hypoglycemia and weight gain may constrain the effort. Problems with hypoglycemia and more difficult titration have led the authors of the ADA/EASD consensus algorithm for the treatment of type 2 DM to discourage use of premixed products during the initial dose-adjustment phases of insulin therapy.¹¹

If we critically analyze what we need from a basal insulin, the choice seems to naturally narrow to the long-acting insulin analogues. Clearly, we should strive for the least hypoglycemia possible.^{6,7} Avoiding excessive weight gain also is desirable.^{6,7} We want insulin action to remain the same day after day (ie, have low variability) in our patients because this helps us titrate to a stable, effective dose with a minimum of hypoglycemia and maximum control. For my patients, I'd like to have the insulin delivered in an easy-to-use, convenient pen device.¹²

Finally, I put a large premium on the simplicity of once-daily dosing. In my opinion, a more complicated regimen lessens the likelihood that primary care will broadly accept the therapy and that patients will be compliant. Is it any surprise that I like coffee that comes in those ready-to-use pouches that you just toss into the coffeemaker and add water? I'd like to keep use of basal insulin just as simple for my patients. Clearly, to satisfy my criteria for an ideal basal insulin, I'm shopping for an insulin analogue—detemir or glargine.

INSULIN ANALOGUES—MORE ALIKE THAN DIFFERENT?

Are insulin detemir and insulin glargine interchangeable? The answer is no, not completely, but they do come closer than any other basal preparations to mimicking human physiology. In many ways, they are similar. Each is available in a simple-to-use, disposable pen delivery system (which is especially important for patients with visual or manual dexterity

problems). The incidence of hypoglycemia is clearly lower with either of these analogues than with NPH or NPH-like insulins. In studies of patients with type 2 DM who were treated unsuccessfully with 1 or 2 oral agents—one study comparing glargine and NPH,¹³ the other comparing detemir and NPH¹⁴—the analogues had significantly lower rates of hypoglycemia, especially at night. In a head-to-head comparison of detemir and glargine in patients with type 2 DM,¹⁵ no significant difference in the incidence of hypoglycemia was noted between the 2 analogues; the study design used forced titration to lower fasting blood glucose levels to 100 mg/dL and achieved an A1C of ~7.1%. This finding is consistent with hypoglycemic findings of other head-to-head studies of glargine and detemir in patients with type 2 DM.¹⁶

Many studies in type 2 DM show that these 2 basal analogues are associated with significantly less weight gain than is NPH insulin.^{14,15} In light of the recent ACCORD data,⁵ weight gain as a result of diabetes treatment has received renewed attention, so the weight impact of our therapies is bound to take on new importance. Although some European data suggest that detemir may result in less weight gain or even weight loss compared to glargine, it is unclear in studies in the United States whether this benefit has actually been observed in patients with type 2 DM who were treated to a goal A1C of 7.0%.^{15,17,18} Clearly, either of these analogues offers the opportunity to introduce basal insulin therapy with less impact on weight than NPH insulin.

How, then, do glargine and detemir differ? At least 4 characteristics differentiate the 2 analogues. First, in head-to-head comparisons of glargine and detemir in patients with type 2 DM,^{15,19} glargine has been used effectively at the indicated once-daily dose, whereas detemir has required twice-daily dosing in ~33% to 50% of patients for optimal glycemic control. Of course, the optimist can turn this around to say that detemir was used to optimal effect as a once-daily dose in ~50% to 67% of patients. In fact, in a trial conducted by Philis-Tsimikas et al,²⁰ the addition of only once-daily detemir to a regimen of oral antidiabetic agents reduced A1C by ~1.5%.

The second difference between detemir and glargine is that these insulins are not equivalent unit for unit. It is widely accepted that detemir must be given in higher unit doses to achieve A1C values similar to those achieved with glargine.²¹ Because the per-unit cost of the 2 analogues is almost equivalent, the economic difference may be of practical importance.

The third difference between the 2 analogues is in their pharmacologic properties, which are quite different. Detemir depends on albumin binding and release for its bioavailability.⁸ Glargine depends on a pH-driven dissociation to provide its release into the bloodstream.²² This difference may not be of great interest to the primary care clinicians who prescribe these drugs for patients with type 2 DM, but it may account for other properties, such as inpatient variability.

Inpatient variability is the fourth difference between the 2 basal insulin analogues, at least in theory. I commented on the inpatient variability of NPH insulin above. In a clamp study comparing detemir and glargine in patients with type 1 DM,⁸ a greater degree of within-subject variability was seen with glargine. It is important to note that although this variability was seen in patients with type 1 DM, a study by Rosenstock et al¹⁵ of nearly 500 patients with type 2 DM did not show significant variability between the 2 analogues. How could that be? Patients with type 1 DM have no forgiving insulin secretory reserve. Most of these patients are 100% dependent on insulin that is administered exogenously. In contrast, patients with type 2 DM have the capacity to contribute (downregulate) some of their own insulin production to complement the insulin they are given. Although inpatient variability may be of importance in the more fragile patients with type 1 DM, it is not clear how relevant this is in our patients with type 2 DM (95% of the diabetic population and the patients who are most likely to be treated by primary care practitioners). My own inclination is that this variability has little clinical impact on the usual type 2 DM population. In summary, then, the main differences in glargine and detemir are once-daily dosing with glargine versus potential twice-daily dosing with detemir and the need for higher doses with detemir than with glargine. Beyond that, for primary care clinicians, the reported differences seem largely theoretical.

SUMMARY

Even the finest coffee bean in the world, if used in the wrong proportion to water, yields a substandard cup of java. The coffee must be used in the right mixture to yield a really satisfying brew. The same principle is true for insulin. Too little produces a weak, ineffective result that doesn't get the job done; too much causes a different set of problems (hypoglycemia and weight gain). It's good when it's balanced. Regardless of the basal insulin chosen, the clinician should be committed to using enough to produce a pleasing result (fasting blood glucose of 100–110 mg/dL) without overdoing it (inducing hypoglycemia or excessive weight gain). A commitment to conscientiously address one of the major components of broken physiology (underproduction of basal insulin in a setting of increased need because of insulin resistance) by adequately replacing what's missing (basal insulin) likely is of greater impact than the actual agent chosen to fill that basal insulin gap. It's all about finding a comfortable and effective therapeutic tool and then routinely and systematically using that tool for the benefit of your patients. And with that thought, I think I'll wander into the kitchen and use my very predictable old coffeemaker to make myself a satisfying cup of joe.

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