What is the Right Insulin Regimen for my Patient?

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What can I do to improve my patient's insulin regimen?

The burden of diabetes mellitus is mainly related to long-term complications. An increasing amount of evidence supports the role of poor metabolic control in the pathogenesis of neurovascular complications. The Diabetes Control and Complications Trial (DCCT) has demonstrated that an effort aimed at tightening blood glucose control can prevent microvascular and neuropathic complications. The DCCT has used a preprandial-basal insulin regimen delivered with multiple daily subcutaneous injections or with an insulin pump. The decreased incidence of macrovascular complications has not reached statistical significance, which was not unexpected considering the low incidence of macrovascular events in this young population (average age being 27 years). It is noteworthy that low-density lipoprotein cholesterol (LDL-C) was reduced by 34% in the intensive treatment group.

In this article:

1. **Improving your patient's insulin regimen.**
2. **Benefits of using fast-acting, short-duration insulin analogues.**
3. **B.I.D. regimens and mixed insulins.**
4. **Disadvantages of intermediate and long-acting insulin preparations.**

The United Kingdom Prospective Diabetes Study (UKPDS) has confirmed, in Type 2 diabetes, the correlation between poor metabolic control and both macrovascular and microvascular complications, as well as the impact of tight blood glucose control on the prevention of these complications. There were no differences in the incidence of complications between patients treated with insulin versus sulfonylurea. In this study, after an initial improvement during the first year, blood glucose then drifted up to baseline levels in the following years, whether the patients were treated with metformin, sulfonylurea or insulin. The insulin regimen, however, was not intensive.

The Kumamoto study has indicated that it is possible, using intensive insulin therapy, to maintain the metabolic improvement during several years. In all of the above-

Practice Pointer

With regular insulin:

There is a delay before plasma insulin levels begin to rise;

Insulin levels peak at two hours, followed by a slow decrease.

Depending upon the dose, the duration of action may last five to eight hours.

The slow onset of action results in high early post-prandial blood glucose peaks, even with increased doses.

The prolonged duration of action induces late (*i.e.,* three to five hours) post-prandial hypoglycemia.

mentioned studies, the metabolic control was improved, but not normalized. One of the obstacles was the occurrence of hypoglycemia.

In the DCCT, there was a clear inverse correlation between the level of hemoglobin A1c (HbA1c) and the incidence of hypoglycemic events, particularly severe hypoglycemia. This is essentially due to the absence of timely matching of insulinemia with blood glucose levels. The use of basal-prandial regimens was an attempt to imitate normal physiologic patterns. Injecting regular insulin before each meal was aimed at improving post-prandial blood glucose control, while bedtime basal long-acting insulin injections were designed to provide a basal level between meals as well as during the night. With conventional insulin preparations, however, it was difficult to get close to the ideal plasma insulin profile. Progress in insulin therapy has been marked by step-by-step improvements of insulin preparations. Using these improved tools, clinical scientists and clinicians have worked and should continue to work on designing and experimenting to achieve better insulin regimens.

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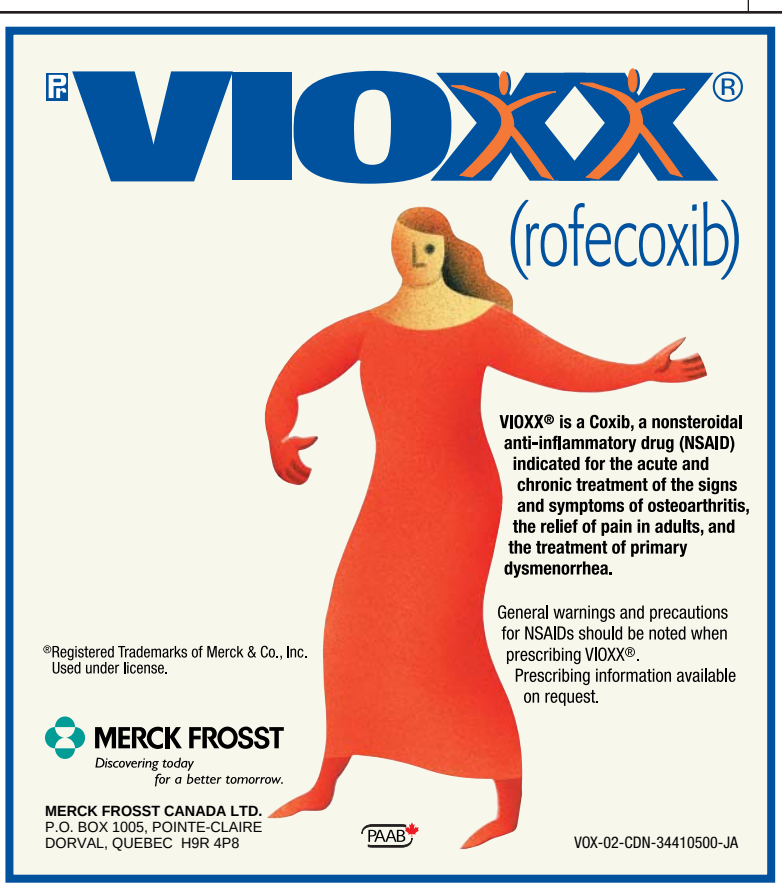


What are the benefits of using fast-acting, short-duration insulin analogues?

Regular, so-called, rapid-acting insulin provides a post-prandial insulin profile that differs from physiologic patterns. In normal subjects, insulin released through the pancreas acts very rapidly at the beginning of a meal. In fact, even before blood glucose begins to rise, the cephalic phase of insulin secretion, *via* the vagal nerve, stimulates insulin release and primes beta cells. Plasma insulin levels peak approximately one hour after the beginning of the meal and decrease to 25% of the peak after two hours. This is the result of a perfect match between insulin release and blood glucose levels.

Practice Pointer

The Benefits of Fast-Acting Insulin Analogues

Provide plasma insulin profiles closer to physiologic profiles;

Lower post-prandial blood glucose peaks;

Allow more flexible and convenient regimens;

Lower incidence of hypoglycemia, particularly nocturnal hypoglycemia; and

Provide better glucose control with CSII

With regular insulin, there is a delay before plasma insulin levels begin to rise, with a peak at two hours, followed by a slow decrease. Depending upon the dose, the duration of action may last between five and eight hours. The slow onset of action results in high early post-prandial blood glucose peaks, even with increased doses. The prolonged duration of action can induce late post-prandial hypoglycemia (*i.e.,* between three and five hours). To prevent the latter, patients are advised to take snacks, thereby adjusting food intake to plasma insulin levels, as opposed to the inverse physiologic process. Ideally, this requires additional blood glucose tests and accurate adjustments to the timing and content of snacks, which is not easily achieved in school-aged patients even very motivated ones.

Studies have shown that, to match blood glucose and insulin peaks, regular insulin should be injected one hour before the beginning of a meal. Even with this ideal timing, the plasma insulin profile is far from physiologic patterns. The much flatter curve results in early hyperinsulinemia, lower insulin peak and, again, late hyperinsulinemia. The main concern has been that hypoglycemic reactions may occur between the injection and the meal. The recommended compromise is to inject insulin 30 to 40 minutes before meals. This is only partly effective and does not prevent the requirement for a snack. In addition, studies have shown that, in real life, as many as 60% of diabetic patients do not comply with this recommendation and end up injecting regular insulin immediately before meals.

To obtain a more physiologic post-prandial insulin profile, insulin analogues have been developed. Two fast-acting short-duration analogues are currently approved for use in Canada: insulin lispro (LysB28, ProB29-human insulin) and insulin aspart (AspartB28-human insulin). The design of these two molecules is relatively similar. The rate-limiting step of regular insulin absorption is the transformation of hexamers

Practice Pointer

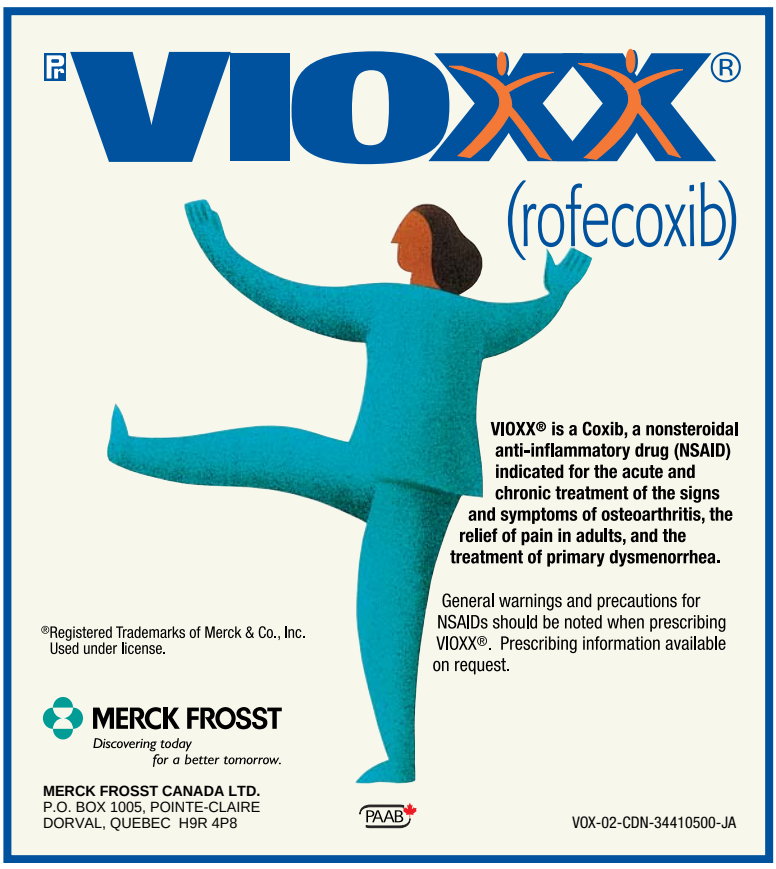
Most studies concur that fast-acting insulin analogues provide a better control of post-prandial blood glucose peaks than regular insulin.

to dimers and then to monomers, the latter being rapidly absorbed. Using genetic engineering techniques, the primary amino-acid sequences of insulin have been changed to modify the polarity and to decrease the auto-association of the molecules. These so-called monomeric insulins are immediately absorbed, providing a plasma insulin profile that closely mimics physiologic profiles: plasma insulin levels peak at 53 (± 30) minutes, as compared to 101 (± 40) minutes for regular insulins, and rapidly fall at 25% of the peak at two hours and then slowly decrease to baseline levels. Naturally, with high insulin doses, this profile is shifted to the right.

Most pharmacodynamic and clinical studies concur that fast-acting insulin analogues provide a better control of post-prandial blood glucose peaks than regular insulin, even when the former is given zero to 15 minutes, and the latter 30 minutes, before meals. In addition, the use of fast-acting analogues results in a lower incidence of hypoglycemia, particularly nocturnal hypoglycemia and severe hypoglycemia. A regimen including insulin injections zero to 15 minutes before meals is more convenient, fostering compliance.

When fast-acting analogues are used in the setting of a preprandial-basal regimen, patients are advised not to take snacks. If they do take a snack containing more than 15 g of carbohydrates, they should take a few units of insulin, depending on the amount of carbohydrates. This is particularly important for Type 1 diabetic patients with no endogenous insulin reserve (*i.e.,* C-peptide-negative patients). Following exercise performed within two hours post-injection and with no dose adjustment, patients are more likely to present a hypoglycemic reaction with a fast-acting insulin analogue than with regular insulin. Insulin doses, therefore, may be decreased if exercise is planned within two hours post-injection.

For physical activities performed at any other time of the day, the occurrence of hypoglycemic reactions is



lower with fast-acting insulin analogues than with regular insulins. Fast-acting analogues are also ideal for insulin supplements, which can be added to the usual premeal and bedtime injections, or even given at any time of the day following unexpectedly high blood glucose results. Faster blood glucose correction may prevent the prolonged drowsiness that sometimes interferes with a patient's normal activities and performance. The short duration of action avoids the overlapping of the supplement's effect with the effect of the following insulin injection, which would make proper insulin dosing difficult.

The faster absorption of fast-acting analogues essentially explains the modified plasma insulin profile following subcutaneous injections. Insulin clearance with analogues and regular insulin is very similar. Therefore, for intravenous use there is no advantage to using analogues over regular insulin.

The use of insulin lispro in subcutaneous insulin infusion (SCII, insulin pumps) is associated with better glycemic control (lower HbA1c) without increasing the frequency of hypoglycemia, as compared to regular insulin. Insulin aspart is also compatible with CSII.

In summary, the use of fast-acting insulin analogues provides plasma insulin profiles closer to physiologic profiles, lower post-prandial blood glucose peaks, more flexible and convenient regimens, and a lower incidence of hypoglycemia, particularly nocturnal hypoglycemia. Tolerance to exercise is better, except in the two hours following the injection, in which case, a proper dose reduction may be performed. These analogues provide better glucose control with CSII.

How should I incorporate B.I.D. regimens and premixed insulins into my patient's treatment?

Most new Type 1, and an increasing number of Type 2 diabetic patients, are being treated with preprandial-basal insulin regimens. For Type 2 diabetics, however, a regimen comprising of a mixture of regular and neutral protamine Hagedorn (NPH) insulins, given twice daily (b.i.d.), remains widely used. The morning regular and NPH insulins control morning and afternoon blood glucose, respectively, while the pre-dinner regular and NPH insulins cover the evening and night blood glucose, respectively. Mixtures prepared by patients before each injection (called a self mix), or premixed insulin vials or cartridges may be used. Mixtures prepared by the patient provide more flexible dose adjustments, specifically giving rise to the possibility of modifying the regular/NPH insulin ratio. Premixed insulins allow the use of insulin pens in the context of a b.i.d. regimen.

Different regular/NPH ratios may be used (*i.e.,* 10/90, 20/80, 30/70, 40/60 and 50/50). The physician may change the ratio occasionally, but premixed insulins are not convenient for day-to-day self-adjustments of insulin doses. Nevertheless, for patients with physical or intellectual limitations, who would not consider self-adjusting their insulin doses, the use of premixed insulin may be convenient.

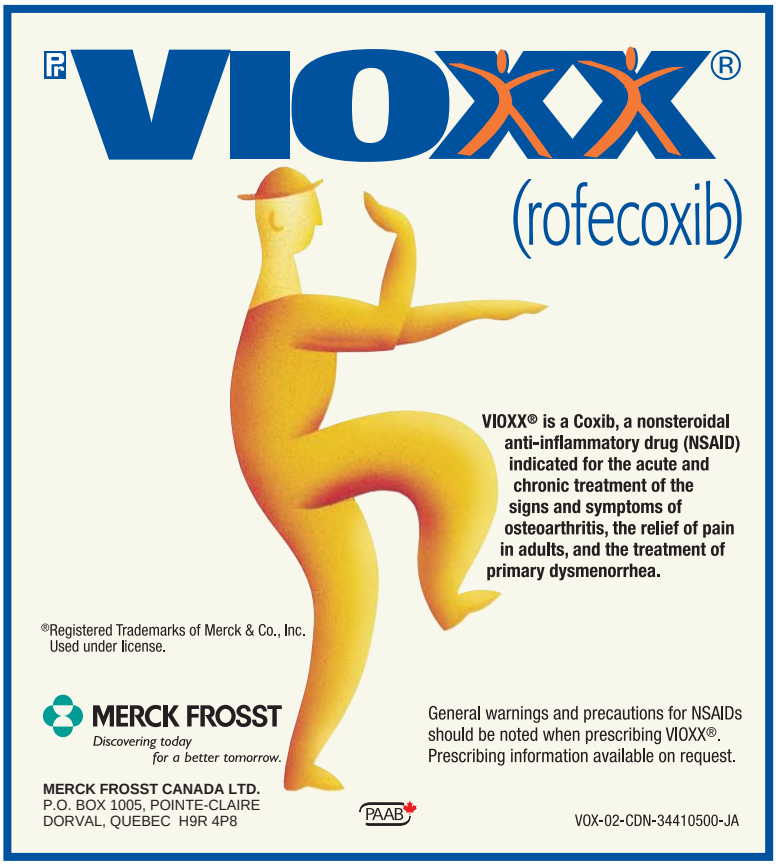
Fast-acting insulin analogues may be mixed with NPH insulin, provided the mixture is prepared immediately before the injection. When used in the context of a b.i.d. fast-

acting analogue/NPH insulin mixture, as compared with a regular/NPH insulin mixture, fast-acting insulin analogues provide better control of post-breakfast and post-dinner blood glucose, while decreasing the incidence of hypoglycemia, particularly nocturnal hypoglycemia.

A premixed preparation of lispro (a fast-acting analogue) with an intermediate, NPH-equivalent insulin is approved for use in Canada. After a few days in the same vial, cartridge or syringe, free lispro molecules will displace protamine-linked regular insulin on NPH molecules, releasing free regular insulin into the solution. These interactions will modify the pharmacokinetics of insulin absorption. In order to avoid this reaction, intermediate insulin molecules have been designed in which lispro, instead of regular insulin, has been linked to protamine. This provides a new intermediate insulin called neutral protamine lispro (NPL). NPL is not marketed alone, but is used to produce a stable 25% lispro/75% NPL premixed insulin preparation, which is equivalent to 30% regular insulin and 70% NPH human insulin, but with the advantages of fast-acting insulin mixtures, as described above.

What are the disadvantages of current intermediate and long-acting insulin preparations? How can long-acting insulin analogues help?

Ideally, basal insulins should provide a peakless plasma insulin profile lasting 24 hours or longer. Pharmacodynamic studies, using glucose clamp techniques, have shown that the plasma insulin peak occurs two to five hours following NPH insulin injection. Typically, when NPH is administered at 10:00 p.m., plasma insulin levels peak between midnight and 3:00 a.m., followed by a relatively rapid decline over the following hours. Insulin sensitivity is maximized between 10:00 p.m. and 3:00 a.m. Therefore, the insulin peak occurs at a time when insulin requirements are lower, which increases the risk of hypoglycemia. In contrast, after 4:00 a.m., insulin requirements increase — the so-called



dawn phenomenon — at a time when plasma insulin levels decrease. This results in early (*i.e.,* midnight to 3:00 a.m.) hypoglycemia with morning rebound hyperglycemia — the so-called Somogyi phenomenon. Numerous patients present a high variability of morning blood glucose. The authors' experience with continuous blood glucose monitoring in Type 2 diabetic patients has shown that the Somogyi phenomenon and the dawn phenomenon are much more prevalent than expected.

Another problem with NPH insulin is its relatively short duration of action (*i.e.,* no longer than 16 hours). When given at bedtime, plasma insulin levels decline to very low levels after 3:00 p.m. This became particularly obvious with the combined use of fast-acting analogues at lunch. In this case, neither the bedtime NPH nor the pre-lunch fast-acting analogue provided enough insulin at the end of the afternoon, which resulted in late afternoon hyperglycemia. A solution to this problem is to add a small dose of NPH in the morning to cover the late afternoon period. It is estimated that approximately 70% of C-peptide-negative patients require this second NPH insulin dose to achieve tight blood glucose control.

The dawn phenomenon is an early-morning increase in plasma glucose concentration

Using an extended insulin zinc suspension provides a more physiologic peakless and prolonged plasma insulin profile. Nevertheless, extended insulin zinc suspension absorption is so erratic and unpredictable that most endocrinologists prefer NPH as a basal insulin. Recent head-to-head comparisons of NPH and an extended insulin zinc suspension in preprandial-basal regimens have confirmed that NPH provides better metabolic control.

In order to overcome these problems, new basal long-acting insulin analogues have been developed. Insulin glargine (21A-Gly-30B-L-Arg-30Bb-L-Arg-human insulin; HOE 901) is currently used in Europe, the U.S., and is approved for use, but not yet available, in Canada.

Pharmacodynamic studies have shown that these insulin analogues provide a peakless and prolonged plasma insulin profile. In clinical trials, regimens using one bedtime insulin glargine injection provide a similar or better fasting plasma glucose than one or two NPH injections a day, with less variability of fasting blood glucose and fewer instances of nocturnal hypoglycemia.

Another feature of the long-acting insulin analogues is the fact that they are solutions and not suspensions. The delayed absorption of NPH and insulins of the lente series results from the addition of molecules, such as protamine and zinc, respectively. These molecules have to be suspended by slowly agitating insulin vials/cartridges before each injection. Inadequate suspension has been shown to induce up to 220% of the variations in insulin absorption. In spite of the fact that suspending insulin before each injection is part of routine education programs, studies have suggested that more than 50% of patients fail to do it properly and regularly. In a number of studies, particularly in Type 2 diabetes, the weight gain was significantly lower with insulin glargine than with NPH.

In contrast, the delayed absorption of long-acting analogues results from a modification of the insulin molecule itself and does not require additional molecules. These clear solutions do not have to be re-suspended. Since the physical appearance of these

analogues is similar to that of regular insulin, special attention must be paid not to confuse them.

In conclusion, the combined use of fast-acting and basal long-acting insulin analogues provides more physiologic plasma insulin profiles and more convenient use. Using these improved tools, clinical scientists and clinicians have worked and should continue to work on designing and experimenting new regimens to optimize blood glucose control and prevent complications. CME

References

1. Holleman F, Hoekstra JB: Insulin lispro N Engl J Med 1997; 337:176-83.
2. Bolli GB, Di Marchi RD, Park GD, et al: Insulin analogues and their potential in the management of diabetes mellitus. Diabetologia 1999; 42:1151-67.
3. Brange J, Owens DR, Kang S, et al: Monomeric insulins and their experimental and clinical implications. Diabetes Care 1990; 13:923-54.
4. Woodworth JR, Arora V, Yang H, et al: Improved postprandial glycemic control with Humalog mix75/25 after a standard test meal in patients with Malone type 2 diabetes mellitus. J Clin Ther 2000; 22(2):222-30.
5. Raskin P, Klaff L, Bergenstal R, et al: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care 2000; 23(11):1666-71.
6. Yki-Jarvinen H, Dressler A, Ziemen M: 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. HOE 901/3002 Study Group. Diabetes Care 2000; 23(8):1130-6.
7. Simpson SH, Toth EL: Expanding the options in insulin therapy: A review of insulin analogues. Can J Diabetes 2002; 26(3):194-205.
8. Melki V, Renard E, Lassmann-Vague V, et al: Improvement of HbA1c and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. Diabetes Care 1998; 21(6):977-82.
9. Zinman B, Tildesley H, Chiasson JL, et al: Insulin lispro in CSII: Results of a double-blind crossover study. Diabetes 1997; 46(3):440-3.
10. Bode BW, Strange P: Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. Diabetes Care 2001; 24(1):69-72.