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REVIEW OF INSULIN THERAPY

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Abstract
The objective of this article is to review the different types of insulin and to explain some of the different dosing regimens that are used. Articles were obtained via a MEDLINE search and product package inserts. There is no one insulin therapy that is best for all patients. Type 1 diabetes patients require insulin therapy to maintain life. Studies support intensive in-sulin dosing in these patients to obtain an A1C of less than 7.0%. Insulin therapy for type 2 diabetes patients may be a little less clear. Long-acting insulin in combination with an oral agent may be just as effective as insulin alone, and in pa- tients who fail oral therapy, a simple insulin regimen is preferred over a complex one.

Key Words: Type 1 diabetes, insulin, A1C, dosing, comparison.

REVIEW OF INSULIN THERAPY

There are approximately 17 million patients in the United States with diabetes. Primary care physicians manage about 39% of the type 1 diabetes patients and 82% of the type 2 diabetes patients. In the United States, 6 to 7 million diabetes patients use human insu- lin or an insulin analog. With the invention of the new insulin analogs, more and more patients are begin- ning to use physiologic insulin replacement or con- tinuous subcutaneous insulin pumps for treatment of their disease.[1]

The hemoglobin A1C (A1C formerly known as HbA1c) goal according to the American Diabetes Asso- ciation is less than 7.0%.[1,2] This type of control, accord- ing to physicians, usually requires intensive insulin therapy.[1] Type 1 diabetes patients require exogenous insulin because they do not produce enough on their own in contrast to type 2 diabetes patients who do not require exogenous insulin for survival, at least ini- tially.[3] Type 2 diabetes patients continue to lose □-cell function despite treatment. Patients with type 2 diabe-tes usually have less than

50% of their normal insulin secretion at diagnosis and after 6 years may only have less than 25%. This decline in □-cell function is the rea- son that many type 2 diabetes patients fail oral therapy and require insulin.[3,4] Insulin therapies may have other advantages for diabetes patients as well. Some studies have shown that □-cell function may be preserved with early insulin therapy. Lipid metabolism and mortality rates after a myocardial infarction may also be improved with the use of insulin.[1,5]

There are several reasons insulin therapy is not used as often as it is needed: possible insulin regimen com- plexity, misconceptions on the costs of insulin therapy; the risks of insulin therapy; patient's feelings of failure on previous treatments; patient's fear of injections, weight gain, and hypoglycemia; and lack of straightfor- ward practice guidelines for the use of insulin.[4,5] This article will attempt to review the different types of insulin and to explain some of the different dosing regimens.

RAPID-ACTING INSULIN

There are 2 rapid-acting insulins approved for use in the United States: insulin lispro suspension (Humalog®) by Eli Lilly and insulin aspart solution (Novolog®) by Novo Nordisk (see Table 1). Both agents are only available by prescription and are human insu- lin analogs that do not self-aggregate in solution like human regular insulin; therefore, they are more rapidly absorbed.[1,6-8]

Lispro

Insulin lispro is chemically known as Lys(B28), Pro(B29), a human insulin analog. Switching the amino acids at positions 28 and 29 on the insulin B- chain makes this insulin. It is made in a nonpathogenic laboratory strain of Escherichia coli bacteria. Lispro in- sulin has an onset of 5 to 15 minutes, peaks in 30 to 90 minutes, and has a duration of action of 3 to 5 hours, but it rarely lasts longer than 4 hours. It is administered via a subcutaneous injection and should be given 5 to 15 minutes before a meal. In children, it may be given immediately after the meal has been eaten. When used in an insulin pump, it should be given immediately be- fore a meal.[1,6,7]

Insulin lispro is clear and should be discarded if it becomes cloudy. This insulin is available as 10-mL vi- als, 1.5-mL and 3-mL cartridges for an insulin pen, and 3-mL disposable pens that contain 100 units/mL. The vial, cartridges, and pens are stable for 28 days, and lispro is stable in an external pump for 48 hours. Insu- lin lispro may be mixed with NPH or ultralente, is sta- ble for 28 days when mixed with NPH, and should be used within 5 minutes when mixed with ultralente. It should not be mixed with insulin-glargine or diluted or mixed with other insulins when used in a pump. It may be mixed with sterile diluent for Humalog®, Humulin® N, Humulin® 50/50 or 70/30, or NPH® Ilentin for use in children. After dilution, it is stable for 28 days at 5°C (41°F) and for 14 days at 30°C (86°F).[6,7]

Aspart

Insulin aspart is made by substituting aspartic acid for proline at position B28 on the insulin chain. This insulin is made using a baker's yeast known as Saccha- romyces cerevisiae. Insulin aspart has an onset of 10 to 20 minutes, has a peak of 1 to 3 hours, and lasts 3 to 5 hours. The Food and Drug Administration approved this drug for subcutaneous injection and infusion.[1,6,8]

Insulin aspart should be given 5 to 10 minutes before a meal. It is available in 10-mL vials, 3-mL cartridges, and 3-mL disposable pens, all of which contain 100 units/mL. This insulin is clear and should be discarded if it looks cloudy. Insulin aspart may be mixed with NPH, but there are no data on mixing it with regular, lente, or ultralente insulin. This insulin should not be mixed or diluted when used in an insulin pump, and should not be mixed with insulin glargine. The insulin vials, cartridge, and pens are stable for 28 days and should be discarded after 48 hours in an insulin pump.[6,8]

Rapid-Acting Insulin Studies

Insulin lispro has several studies to support its use in patients with diabetes. One of the major side effects of insulin therapy is hypoglycemia, especially during sleep. One of the principal things that have been stud- ied with insulin lispro is the incidence of hypogly- cemia when it is used in an intense insulin regimen. There are several studies that have been conducted investigating the incidence of hypoglycemia in type 1 di- abetes patients (formerly insulin-dependent diabetes mellitus patients) who use insulin lispro in combina- tion with NPH or ultralente as the basal insulin. These studies all found that insulin lispro was associated with less hypoglycemia, especially nocturnal hypo- glycemia.[9-12]

Bastyr et al performed a study in type 2 diabetes pa- tients to determine the safety and efficacy of insulin lispro plus a sulfonylurea in those who had failed pre- vious oral therapy with a sulfonylurea alone. Patients were randomized to insulin lispro plus sulfonylurea, bedtime NPH plus sulfonylurea, or lispro plus bedtime NPH. The study found a significant difference in A1C for lispro plus sulfonylurea (–1.60% ± 1.27%) com- pared to NPH plus sulfonylurea (–1.21% ± 1.21%), with the largest improvement seen in the lispro plus sulfonylurea group (P = .003). The authors concluded the insulin lispro plus sulfonylurea was an effective al- ternative in patients who have failed sulfonylurea ther- apy alone.[13]

There have also been a few studies that have looked at the efficacy of insulin lispro as compared to regular insulin in both type 1 and type 2 diabetes patients. These studies used long-acting insulin in combination with either insulin lispro or regular insulin before meals. There was no significant difference in glycemic control or hypoglycemic events in either group of pa- tients, although the incidence of nocturnal hypogly- cemia seems to be less in the lispro group.[14-16]

Other studies have investigated the use of insulin lispro versus regular insulin in insulin pumps in type 1 diabetes patients. The studies found that insulin lispro was associated with lower A1Cs. However, fasting glu- cose values were similar between the 2 groups, but postprandial glucose levels were lower in the lispro group. The authors concluded that insulin lispro had better glycemia control than regular insulin with no difference in adverse effects.[17-19]

There have been a number of studies of insulin aspart in type 1 diabetes patients. Three studies have compared insulin aspart with regular insulin. All 3 studies dosed insulin aspart or regular insulin before meals plus dosed NPH as the basal insulin. The studies found that postprandial glucose levels were signifi- cantly improved in patients receiving insulin aspart with no increased risk of hypoglycemia. There was also a lower A1C in patients treated with insulin aspart than with regular insulin. The authors concluded that insu- lin aspart improved glycemic control compared to reg- ular insulin.[20-22]

One study compared insulin aspart and insulin lispro in type 1 diabetes. This study was a crossover clamp trial, which found the 2 insulins equivalent in terms of pharmacodynamic and pharmacokinetic prin- ciples. A1C results were not reported in this study.[23]

Conclusion

In conclusion, there are several advantages to the use of the rapid-acting insulins. One advantage is a faster onset of action, which allows the insulin to be taken closer to meals. A second advantage is the shorter time to peak activity, which allows for better control of postprandial blood sugars. The last advantage to this insulin is less risk of nocturnal hypoglycemia. The dis- advantage of rapid-acting insulin is the shorter dura- tion of action, which means that multiple injections are needed throughout the day for good glycemic control.

SHORT-ACTING INSULIN

There are 4 short-acting insulins: regular insulin (Humulin® R by Eli Lilly and Novolin® R by Novo Nordisk), buffered regular insulin (Velosulin® BR by Novo Nordisk), and pork regular

insulin (Iletin® II Reg- ular) (see Table 1). Beef insulin is no longer Food and Drug Administration approved and is no longer made for use in the United States. Humulin® R, Novolin® R, and Velosulin® BR are human rDNA insulins and Iletin® II Regular is pork insulin.[1,6]

Humulin® R and Novolin® R

Humulin® R and Novolin® R are made of zinc- insulin crystals dissolved in a clear fluid. Humulin® R is made using the E. coli bacteria, and Novolin® R is made using a baker's yeast called S. cerevisiae. Humulin® R and Novolin® R 100 units/mL are avail- able without a prescription and Humulin® R 500 units/ mL with a prescription. Regular insulin has an onset of action of 30 to 60 minutes,a peak of 1 to5 hours, and a duration of 6 to 10 hours, maybe longer with the 500 units/mL insulin. Both Humulin® and Novolin® insulin may be administered subcutaneously or in- travenously (unlabeled use). The 500 units/mL regu-lar insulin may only be administered subcutaneously. When given intravenously, the insulin acts almost immediately.[1,6,24,25]

Both types of insulin should be administered 30 minutes prior to a meal, and when used in an insulin pump, the bolus should be given 20 to 30 minutes be- fore a meal. The 100 units/mL Humulin® R is available in a 10-mL vial, and the 500 units/mL is available in a 20-mL vial. Novolin® R is available in a 10-mL vial, 1.5- and 3-mL cartridges, 1.5-mL disposable pen, and a 3-mL Innolet® device. The 100 units/mL insulin for both manufacturers is clear and colorless, whereas the 500 units/mL may be straw colored. Humulin® and Novolin® R may be mixed with NPH, and the mixture is stable at room temperature for 1 month and in the re- frigerator for 3 months. When regular insulin is mixed with lente or ultralente, the onset of regular insulin may be delayed and not reach equilibrium for 24 hours; therefore, this combination should not be used unless the patient has been stable on this regimen in the past. Regular insulin should not be mixed with insulin glargine. Regular insulin may be mixed with water for injection, mixed with 0.9% sodium chloride for injec- tion, and used within 24 hours in an insulin pump. Regular insulin is stable at room temperature when mixed with Lilly regular insulin diluent for 1 month. Humulin® R vials are good for 30 days, and Novolin® vials, pens, and 1.5-mL cartridges are stable for 1 month, whereas the 3-mL cartridges and Innolet® de- vice are stable for 28 days.[6]

Buffered Regular

Buffered regular insulin is human rDNA insulin that is available without a prescription. It has an onset of ac- tion of 30 to 60 minutes,a peak of 1 to3 hours, and a du- ration of about 8 hours. Buffered regular insulin may be given subcutaneously and intravenously (unlabeled) and is approved for use in insulin pumps. Buffered in- sulin should be given 30 minutes prior to a meal and when used in an insulin pump should be bolused 20 to 30 minutes prior to a meal. This insulin is available as 100 units/mL in 10-mL vials.[6] Buffered regular insulin is clear and colorless and should be discarded if it be- comes cloudy. Buffered insulin should not be mixed with other insulins. The vial is stable for 28 days and can be used for up to 48 hours in insulin pumps.[6]

Pork Regular Insulin

Pork regular insulin is available without a prescrip- tion. Its onset of action may be more rapid than human insulin, its peak may be faster than human insulin, and

Table 1: Pharmacokinetics of Available Insulin Products

Insulin	Onset	Peak	Duration	Appearance
Lispro	5-15 minutes	30-90 minutes	3-5 hours	Clear
Aspart	10-20 minutes	1-3 hours	3-5 hours	Clear
Regular insulin	30-60 minutes	1-5 hours	6-10 hours	Clear
Buffered regular insulin	30-60 minutes	1-3 hours	8 hours	Clear
Pork insulin	More rapid than regular	Faster than regular	4-12 hours	Clear
Lente	1-3 hours	6-14 hours	16-24 hours	Cloudy
NPH	1-2 hours	6-14 hours	16-24+ hours	Cloudy
Glargine	1.1 hours	None	~24 hours	Clear
Ultralente	4-6 hours	8-20 hours	> 24 hours	Cloudy
Novolog® 70/30	More rapid than Novolin® 70/30	1-4 hours	15-18 hours	Cloudy
Humalog® 75/25	More rapid than Humalog® 70/30	1-6.5 hours	24 hours	Cloudy
Humulin/Novolin 70/30	30-60 minutes	2-16 hours	18-24 hours	Cloudy

its duration is 4 to 12 hours. It may be administered subcutaneously or intravenously (unlabeled). The in- sulin should be injected 30 minutes before a meal, and when used in an insulin pump, the bolus should be given 20 to 30 minutes prior to a meal. The insulin is available in 10-mL vials at 100 units/mL.[6] Pork insulin may only be mixed with Iletin® II Lente if given imme- diately. It may also be mixed with NPH and ultralente. It should not be mixed with insulin glargine. The insu- lin is stable for 1 month at room temperature when it is mixed with Lilly regular insulin diluent. The vials are also stable for 1 month at room temperature.[6]

Conclusion

There are some advantages and disadvantages to the use of regular insulins. One advantage is the ability to mix the insulin with a variety of other insulins (NPH, Lente, ultralente). The second advantage is the longer duration of action, which may allow the insulin to be given only twice daily. One disadvantage to regular in- sulin is a larger risk of hypoglycemia, especially when combined with other insulins with a longer duration of action. A second disadvantage is hypersensitivity reactions with the pork insulin.

INTERMEDIATE-ACTING INSULIN

There are 2 main types of intermediate-acting insulins: lente and NPH (see Table 1). There are 3 types of lente insulin: Novolin® L by Novo Nordisk, Humulin® L by Eli Lilly, and Iletin® II Lente by Eli Lilly. NPH comes in 3 types as well: Novolin® N by Novo Nordisk, Humulin® N by Eli Lilly, and Iletin® II NPH by Eli Lilly. Humulin® L is a human amorphous and crystalline suspension of zinc and acetate buffers with a slower onset and longer duration of action than regular insulin. Like the other Humulin® products, it is made with the bacteria E. coli. Novolin® L is human in- sulin as well made from the baker's yeast S. cerevisiae. Iletin® II Lente is pork insulin. Humulin® NPH is a crystalline suspension of protamine, zinc, and human insulin with a slower onset and longer duration of ac- tion than regular insulin. Humulin® NPH is made with a bacterium just like the other Humulin® products. Novolin® NPH is also a suspension of protamine and zinc and is made with the same baker's yeast as other Novolin® products. Iletin® II NPH is made of pork.[6,26-28]

Lente (Insulin Zinc Suspension)

The onset of the human lente insulins is 1 to 3 hours, the peak is 6 to 14 hours, and the duration of action is 16 to 24 hours. The onset of the pork insulin may be more rapid than the human insulin, the peak is the same, and the duration is slightly greater than 24 hours. All of the insulins should only be given subcutane- ously and must be resuspended before injection. The insulin should be injected 15 minutes prior to a meal when it is mixed with rapid-acting insulin and 30 min- utes prior to a meal when mixed with regular insulin. All 3 insulins are available in 10-mL vials at 100 units/ mL.[1,6] All of these insulins are cloudy. They should not be mixed with regular insulin unless the patient is al- ready stable on the regimen because it delays the onset of short-acting insulin. Lente can be mixed with ultralente but should not be mixed with NPH or insulin

glargine. Lente is stable for 1 month at room tempera- ture when mixed with Lilly Lente insulin diluent. All of the vials are stable for 1 month at room temperature.[6]

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NPH (Isophane Insulin Suspension)

The human insulins have an onset of action of 1 to 2 hours, a peak of 6 to 14 hours, and a duration of 16 to 24+ hours. The pork insulin has a faster onset of action, the same peak, and a longer duration of action. All 3 insulins may be administered subcutaneously but must be resuspended before injection. The insulin should be administered within 15 minutes of a meal when given in combination with a rapid insulin and within 30 minutes when mixed with regular insulin. Novolin® N is available as 10-mL vials, 1.5- and 3-mL cartridges, 1.5-mL disposable pens, and a 3-mL Innolet® device, which all contain 100 units/mL. Humulin® N is available as a 10-mL vial and a 3-mL disposable pen, both containing 100 units/mL. Iletin® II NPH is also available as a 10-mL vial containing 100 units/mL.[1,6]

All 3 insulins are cloudy and can be mixed with aspart, lispro, or regular insulin. All 3 types of insulin are stable for up to 1 month at room temperature after being mixed with Lilly NPH insulin diluent. NPH insu- lin should not be mixed with lente, ultralente, or glargine. Novolin NPH is stable for 30 days in the vial, 14 days in the 3-mL cartridge and Innolet device, and 7 days for the 1.5-mL pen. Humulin® NPH is stable for 1 month in the vial and 14 days in the 3-mL pen. Iletin® II NPH isstable for 1 month inthe vial at room temperature.[6]

Conclusion

There are some advantages and disadvantages to these insulins. One advantage is the long duration of action that allows for twice-daily dosing and in some cases even once-daily dosing (see Regimen section later in this article). Another advantage is the ability to mix these insulins with the other shorter acting insu- lin, thus reducing the number of injections a patient must administer. One disadvantage of these insulins is the twice-daily dosing in most patients to obtain 24- hour glucose control. Another disadvantage is the peak and trough concentrations that occur with these agents because of the lack of 24-hour control. These peak and troughs allow the risk for hypoglycemia and hyperglycemia. The last disadvantage is the hypersen- sitivity reaction that may occur when using the pork insulin.

LONG-ACTING INSULIN

There are 2 long-acting insulins: insulin glargine (Lantus® by Aventis) and ultralente (Humulin® U by Eli Lilly) (see Table 1). Insulin glargine is human insu- lin that has glycine in place of asparagine in position A21 and 2 arginines added to the C-terminus of the B- chain. It forms a microprecipitate in the subcutaneous tissue. The crystals then dissolve, releasing the insulin slowly, thus making insulin glargine a long-acting product. Insulin glargine is produced in the bacteria E. coli. Ultralente is a crystalline zinc suspension of hu- man insulin. It is made in a similar way to the other Humulin® products.[1,6,29-31]

Insulin Glargine

Insulin glargine is available by prescription only. It is human insulin with an onset of action of 1.1 hours, no significant peak, and duration of 24 hours. It may be administered by subcutaneous injection but not intra- muscularly. When insulin glargine is administered in- travenously, it has an identical response to regular hu- man insulin given intravenously. The dose of glargine should be reduced by 20% when switching from a twice-daily NPH, but no adjustment needs to be made when switching from a once-daily NPH or ultralente. The insulin is clear (different from the intermediate- acting or other long-acting insulins), and no shaking is necessary before administration. Insulin glargine has a low pH, which may lead to burning at the injection site.[1,6,29,31] Insulin glargine is administered once daily (either morning or bedtime) and is available as 100 units/mL 10-mL vials. Insulin glargine should not be mixed with other

insulins due to its low pH. The insu- lin vial is stable for 28 days.[6,29,31]

Ultralente

Ultralente is human insulin that is available without a prescription. It has an onset of action of 4 to 6 hours, a peak of 8 to 20 hours, and a duration of 24 to 28 hours. The duration of action may be somewhat dose depend- ent. The insulin should be cloudy prior to administra- tion and should be resuspended before injection.[1,6] Ultralente should be injected within 15 minutes prior to a meal when mixed with rapid-acting insulin and 30 minutes prior to a meal when mixed with regular insu- lin. The insulin is available in 10-mL vials that contain 100 units/mL. Ultralente may be mixed with insulin lispro (need to inject within 5 minutes of mixing), regu- lar insulin, and lente insulin. Ultralente is stable at room temperature for 1 month and in the refrigerator for 3 months when mixed with lente. When mixed with Lilly lente insulin diluent, ultralente is stable for 1 month at room temperature. Ultralente should not be mixed with NPH. The 10-mL vials are stable for 1 month at room temperature.[6]

Long-Acting Insulin Studies

A study by Tunbridge et al compared ultralente to lente in a twice-daily injection regimen. Patients were randomized to receive either ultralente or lente twice daily in combination with regular insulin. The study found that fasting glucose levels were significantly lower in the ultralente group than in the lente group (118.9 ± 9.0 mg/dL [6.6 ± 0.5 mmol/L] vs. 147.7 ± 9.0mg/dL [8.2 ± 0.5 mmol/L], $P < .05$); however, the A1Cs were the same in the two groups (9.3% ± 0.2%). The in- cidence of hypoglycemic events was also significantly higher in the ultralente group (0.38 ± 0.10 vs. 0.09 ± 0.04 events per patient month, $P < .02$). The authors concluded that ultralente offers no clinical advantage over lente in patients with higher fasting glucose con- centrations or marked nocturnal hypoglycemia.[32]

There have been several studies that have investi- gated the incidence of hypoglycemia in patients who were given insulin glargine. No significant change in A1C was noted in either study, but there was an overall decrease in the incidence of hypoglycemia.[33,34]

Other studies have compared regimens using insu- lin glargine to more traditional regimens using NPH. Patients were randomized to receive NPH either once or twice daily or insulin glargine once daily, both in combination with insulin lispro or regular insulin. Overall, the studies showed a significant decrease in fasting blood glucose levels; however, there was no significant change in A1C seen in 2 studies, and 1 study found a significant decrease in A1C in the glargine group. There was also no difference seen in the overall incidence of hypoglycemia in all 3 studies, but 2 of the studies showed a slight decrease in nocturnal hypoglycemia. The authors concluded that insulin glargine was safe and at least as effective as NPH in managing patients with diabetes.[35-37] A study con- ducted by Yki-Jarvinen et al studied insulin glargine versus bedtime NPH in patients also receiving oral agents. The study found no change in A1C between the two groups (8.3% ± 0.1 vs. 8.2% ± 0.1), but there was less nocturnal hypoglycemia seen in the glargine group (9.9% vs. 24.0% of all patients, $P < .001$). The postdin- ner glucose levels were also significantly lower in the glargine group compared to the NPH group (178.4 ± 3.6 mg/dL [9.9 ± 0.2 mmol/L] vs. 192.8 ± 5.4 mg/dL [10.7 ± 0.3 mmol/L], $P < .02$). The authors concluded that insu- lin glargine should be used instead of NPH in insulin regimens in patients with type 2 diabetes.[38]

Conclusion

One advantage is the long duration of action of ultralente, which allows for possible once-daily dosing in patients. A disadvantage to ultralente is the possibil- ity that its effects may not last 24 hours depending on the patient's dose or individual kinetics.

There are several advantages and disadvantages to the use of insulin glargine. Advantages of glargine in- clude once-daily administration, lack of insulin peak, 24-hour duration of action, and reduced incidence of nocturnal hypoglycemia. Disadvantages include cost, pain on

injection, and inability to mix it with other types of insulin.[31]

INSULIN MIXTURES

There are 4 premixed insulin products (see Table 1). The first is Novolog® Mix 70/30 by Novo Nordisk. It contains 30% insulin aspart and 70% insulin aspart protamine (long-acting insulin similar to NPH). An- other insulin premix is Humalog® Mix 75/25 by Eli Lilly. This insulin contains 25% insulin lispro and 75% insulin lispro protamine (long-acting insulin sim- ilar to NPH). The third premixed insulin product is made of 70% NPH and 30% regular (Humulin® 70/30 by Eli Lilly and Novolin® 70/30 by Novo Nordisk). The last premixed insulin available is Humulin® 50/50 by Eli Lilly that contains 50% NPH and 50% regular. All of the insulins should be cloudy prior to use.[1,6,39-42]

Insulin Aspart 30% and Insulin Aspart Protamine 70%

Novolog® Mix is available by prescription only. It is human insulin with an onset of action that is faster than Novolin® 70/30, has a peak of 1 to 4 hours, and has a duration of 15 to 18 hours (maximum of 24 hours).[6,42] Novolog® Mix should only be administered subcuta- neously and must be resuspended prior to injection. It should be given 10 to 20 minutes prior to a meal. It is available in 10-mL vials, 3-mL cartridges, and 3-mL disposable pens, all containing 100 units/mL of insu- lin. Novolog® Mix should not be mixed with any other type of insulin. The pens and vial are stable for 28 days, and the 3-mL cartridge is stable for 14 days.[6,42]

Insulin Lispro 25% and Insulin Lispro Protamine 75%

Humalog® Mix is human insulin available by pre- scription only. It has an onset of action that is faster than Humulin® 70/30, a peak of 1 to 6.5 hours, and a duration of up to 24 hours. Humalog® should only be administered subcutaneously and must be resuspend- ed prior to use. It should be given 15 minutes prior to a meal. It is available in 100 units/mL 10-mL vials and 3-mL disposable pens. Humalog® Mix should not be mixed with any other type of insulin and is stable for 1 month at room temperature after dilution with Lilly NPH diluent. The vial is stable for 28 days, and the pens are stable for 10 days.[6,41]

NPH and Regular Combinations

There are 2 insulin combinations of 70% NPH and 30% regular made by 2 different companies. Both com- binations are available without a prescription. These 2 combinations are human insulins with an onset of ac- tion of 30 to 60 minutes, a peak of 2 to 16 hours, and a duration of 18 to 24 hours. Both agents should only be used subcutaneously and must be resuspended prior to injection. The insulins should be given 30 minutes prior to meals. Humulin® 70/30 is available in 10-mL vials and 3-mL disposable pens, all containing 100 units/mL of insulin. Novolin® 70/30 is available in 10- mL vials, 1.5- and 3-mL cartridges, 1.5-mL disposable pens, and a 3-mL Innolet® device, all of which contain 100 units/mL of insulin. These insulins should not be mixed with other insulins. Humulin® 70/30 may be mixed with Lilly NPH insulin diluent and is stable for 1 month at room temperature. A vial of Humulin® 70/30 is stable for 28 days, and the pen is stable for up to 10 days. A vial of Novolin® 70/30 is stable for 30 days, the 1.5-mL cartridges are stable for 7 days, and the 3-mL cartridges and Innolet® device are stable for 10 days.[6] The other NPH-regular mixture is 50% NPH and 50% regular (Humulin® 50/50). This insulin is avail- able without a prescription. It is human insulin with an onset of 30 to 60 minutes,a peak of 2 to 5.5 hours, anda duration of 18 to 24 hours. It should only be given sub- cutaneously and must be resuspended prior to use. It must be given 30 minutes prior to a meal and may not be mixed with any other insulin. It may be mixed with Lilly NPH insulin diluent and is stable for 1 month at room temperature. Humulin® 50/50 is available in 10- mL vials containing 100 units/mL and is stable for 28days.[6]

Studies of Combination Therapy

The Humalog® and Novolog® Mix have been stud- ied in a few trials compared to their counterparts of reg- ular and NPH combination. The studies showed a lower 2-hour postprandial level with the Humalog/ Novolog after breakfast and dinner. The risk of hypoglycemia was similar between the 2 groups. There was no significant difference in A1C between the groups. The authors concluded that the postprandial glucose levels were better with Humalog/Novolog, but overall control and risk of hypoglycemia were similar between the 2 groups.[43-45]

Conclusion

There are several advantages for the use of premixed insulins. One advantage is the ability to use a combina- tion of regular/lispro insulin with long-acting insulin without the patient having to draw up the individual insulins. Another advantage is a cheaper cost due to the patient only having to buy one form of insulin. A disadvantage is the fixed ratio of regular:long-acting in- sulin, which does not allow for easy dose changes.

DOSING REGIMENS

Insulin dosing is very patient specific, and there is no one way that will work best for all patients. The 2 main methods of insulin dosing are "nonphysiologic" and "physiologic." Nonphysiologic insulin regimens do not mimic normal □-cell function, whereas physio- logic regimens try to mimic normal insulin secretion. The key difference is a physiologic regimen gives basal insulin separate from bolus insulin. The basal insulin is usually given once or twice daily, and the bolus insu- lin is usually given before each meal.[1]

For a long time, NPH insulin dosed twice daily was used as the basal insulin, and regular insulin was used for the bolus dosing. However, regular insulin's dura- tion of action makes it basal insulin until after lunch, leading to an increased risk of morning hypoglycemia. With the invention of shorter acting insulins (lispro and aspart) and a new 24-hour "peakless" insulin (glargine), the old NPH-regular regimen is being recon- sidered. When a basal and bolus insulin combination is used, it increases a patient's flexibility and even may allow the patient to skip or change meal times depend- ing on the combination chosen. One disadvantage to this new physiologic approach is the need for the pa- tient to administer more than one injection a day. Many patients feel, however, that the flexibility of this new dosing strategy far outweighs having to administer more injections. One advantage to this new regimen is easier dose adjustments because the basal and bolus doses can be changed separately.[1]

How do you determine if a nonphysiologic or physi- ologic dosing regimen is right for your patient? The first thing to consider is the type of diabetes your patient has. Is he or she type 1 or type 2? Little data exist com- paring nonphysiologic regimens in type 1 diabetes pa- tients. However, there are data comparing the physio- logic regimens in type 1 diabetes patients. Some studies have compared NPH as the basal insulin with rapid-acting insulin as the bolus. The data from these studies have been mixed in the type 1 patient popula- tion. No change was seen in the overall A1Cs because the lower postprandial blood sugars are offset by higher preprandial blood sugars and the overnight hypergly- cemia.[1,46] There have been some studies that have in- vestigated using ultralente over NPH because of its lon- ger duration of action; however, when compared to lente insulin, it mildly improved glucose levels but also increased the risk for hypoglycemia. With the ad- dition of insulin glargine, one would expect better re- sults because of its peakless action. Studies have shown a decrease in the incidence of hypoglycemia in patients with type 1 diabetes but no reduction in A1Cs. When insulin glargine is compared with NPH directly, there is no change seen in A1Cs, but there are fewer hypoglycemic episodes. When patients are changed from a nonphysiologic to a physiologic regimen (ie, multiple injections or a pump), they need approxi- mately half of their insulin as the basal insulin. When initially starting the regimen, patients should only use 20% of the calculated 50% basal dose at first to prevent hypoglycemia. The dosage can be adjusted thereafter.[1]

Patients with type 2 diabetes require a different ap- proach. When choosing an insulin regimen,

the inten- sity of the regimen needed for good glucose control needs to be tempered with the cost and ease of the regi- men. Most type 2 patients prefer the most simple regi- mens possible. Studies have shown that patients would prefer to use insulin glargine to NPH, ultralente to twice-daily NPH, and insulin pens or premixed in- sulin to having to draw up the dose themselves. Type 2 patients may have the following options for treatment: oral antidiabetic agents in combination with insulin or just strictly insulin therapy.[1]

When oral antidiabetic agents are continued, NPH or insulin glargine is initially started at bedtime. Fritsche et al investigated the use of insulin glargine in the morning versus glargine at bedtime or NPH at bed- time, all in combination with glimepiride once daily. This study found that glycemic control was signifi- cantly improved in all 3 regimens, but the A1C was significantly more improved in the morning glargine group (–1.23% morning glargine vs. –0.83% bedtime NPH, P = .0002; –1.29% morning glargine vs. –1.01% bedtime glargine, P = .009). More patients achieved an A1C less than 8.0% with insulin glargine (morning or bedtime) versus NPH. Insulin glargine patients also had significantly less nocturnal hypoglycemia. This study shows that insulin glargine is effective for type 2 diabetes patients when given in the morning and in combination with glimepiride.[47] Metformin is also a good choice as an oral antidiabetic agent to use in com- bination with insulin because it causes less weight gain, has the ability to lower insulin doses, and theoret- ically has no potential to cause hypoglycemia. Thiazolidinediones are another class of agents that may be useful in combination with insulin because of their insulin-sensitizing ability. However, they are more expensive than other oral antidiabetic agents, re- quire frequent liver function monitoring, may cause weight gain and edema, and should not be used in pa- tients with class III or IV heart failure. Studies that have compared combination metformin-insulin therapy to thiazolidinediones-insulin therapy have shown a simi- lar reduction in A1C in both groups, but hypoglycemia occurs less frequently in the metformin-insulin group.[1] The combination of metformin and insulin has also been studied and compared to glyburide and insulin; glyburide, metformin, and insulin; and 2 doses of insu- lin. The study found that the combination of metformin and insulin prevented weight gain and was considered to be superior in glycemic control. The A1Cs in the metformin-insulin patient group progres- sively decreased over time unlike the other patient groups (–2.5% ± 0.4). The difference seen in the A1Cs was thought to be significant. The frequency of hypoglycemia was also significantly decreased in the metformin-insulin group (P < .05 compared to other groups).[48] A study published in 1992 in the New Eng- land Journal of Medicine showed the combination of oral antidiabetic agents and insulin to be just as effec- tive in type 2 diabetes patients as multiple daily insulin injections. This study also found that patients who used sulfonylurea or metformin in combination with NPH insulin in the evening had similar improvement in glycemic control as patients who used the same combination with NPH in the morning, 2 insulin injections a day, or multiple insulin injections.[49]

Many type 2 diabetes patients, however, may re- quire treatment with insulin alone due to loss of □-cell function altogether over time. Patients who are prone to hypoglycemia appear to benefit from insulin glargine given at bedtime. Insulin glargine also leads to better postprandial control and less weight gain than NPH, but it is about twice the cost.[1] A recent study pub-lished in Diabetes Care showed that insulin glargine is safe and effective whether it is given before breakfast, before dinner, or at bedtime, which may allow for more flexibility in patients.[50] Ultralente may also be an op- tion, but it is associated with more hypoglycemia and higher A1C than twice daily NPH.[1,51] Premixed insulin may be an option for those who cannot use a combina- tion of an oral antidiabetic agent and long-acting insu- lin and who do not want to administer multiple shots throughout the day. Patients who are not controlled us- ing premixed insulins may need to be considered as candidates for multiple injections throughout the day. Another thing to keep in mind is that type 2 diabetes patients often require higher doses of insulin than a type 1 patient to reach the same A1C level due to insu- lin resistance.[1]

CONCLUSION

There is no single “best” insulin regimen for all pa- tients with diabetes. Patients with type 1 diabetes re- quire insulin therapy to sustain life. Studies support intensive insulin regimens to attain an A1C of less than 7.0%. Insulin therapy in type 2 diabetes patients is a lit- tle less clear. It is still ambivalent as to the best time to start insulin therapy and what regimen to start with. Recent studies show that use of long-acting insulin, preferably insulin glargine, in combination with an oral agent may be just as effective as insulin alone. One point that seems to be clear when treating type 2 pa- tients who fail oral antidiabetic therapy is that simple is better. A simplistic insulin regimen is preferred to help prevent the risk of hypoglycemia or other compli- cations of insulin therapy and to increase patient satisfaction by making their lifestyles as simple as possible.

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