Prescribing insulin in type 1 diabetes mellitus: an update for general practitioners

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Introduction

The pancreas in a non-diabetic patient constantly secretes a small amount of insulin (basal secretion). After meals, a larger amount of insulin is secreted (bolus secretion) to cope with the increased blood glucose that occurs following a meal.

The goal of insulin therapy in diabetics is to mimic this secretion pattern to provide enough insulin throughout a 24-hour period to meet the basal requirements and to deliver higher boluses of insulin to meet the glycaemic effect of meals. To achieve good diabetes control, an individually tailored insulin treatment regimen is required.

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TYPES OF INSULIN

Insulin was discovered in 1921 by Dr Frederick G Banting and Charles Best. It was first administered to a patient in 1922 and, since then, has been commercially available for the treatment of diabetes mellitus. Significant developments in insulin research have been the advent of recombinant DNA techniques and devices, allowing for easier administration of insulin.

Recombinant DNA technology has provided the means to produce large amounts of insulin identical to human insulin, thus eliminating the need to obtain insulin from animal sources (beef and pig). The various types of insulin differ in their pharmacokinetic profiles (Table I). The following discussion has been limited to human insulin, as it is readily available in South Africa.

Conventional insulin

Regular (soluble)

This form of insulin consists of zinc crystals that self-associate into dimers and then hexamers after subcutaneous injection. The hexameric form is more slowly absorbed, thereby delaying the onset of action (see Figure 1 A). Examples are Actrapid (Novo Nordisk) and Humulin R (Lilly).

Neutral protamine Hagedorn (NPH)

These insulins are crystalline suspensions of regular insulin complexed with protamine and zinc (NPH). This complex has a delayed absorption, thus delaying the onset of action and providing an intermediate-acting insulin (see Figure 1 B). Isophane NPH insulins are extensively used in children, mainly because of their suitability for mixing with soluble insulin. The pharmacokinetic profiles of these insulins make them suitable for twice-daily regimens and for the pre-bedtime dosage in basal bolus and three-times daily regimens. Examples are Protophane and Humulin N.

Lente and Ultralente

These preparations are complexed with zinc crystals only. As with NPH, the complex has a delayed absorption, thus delaying the onset of action and providing an intermediate-acting insulin. These preparations have largely been superseded by the longer-acting insulin analogues.

Premixed insulin

These are fixed ratio mixtures of soluble and isophane (NPH) insulins. They are useful in adults and pre-pubertal children, particularly when compliance is a problem. There is evidence of poorer metabolic control in adolescents using these insulins, as they remove the flexibility offered by separate adjustments of the two types of insulin.

Insulin analogues

Recombinant DNA technology, as well as the wish to emulate normal insulin secretion, has led to the development of analogues to human insulin.[1] These analogues are comparable to conventional insulin in their ability to bind the insulin receptor; however, due to modifications in the β- and/or α-chain of the insulin molecule, the insulin ana-

Table I: Pharmacokinetics of the various types of insulin

Insulin	Source	Onset	Peak	Duration
Rapid-acting				
Analogues				
Insulin Lispro (Humalog)	Recombinant DNA	15 mins	60 mins	3-4 hours
Insulin Aspart (NovoRapid)	Recombinant DNA	10 mins	45 mins	3-5 hours
Insulin Glulisine (Apidra)	Recombinant DNA		50-60 mins	3-4 hours
Regular (soluble)				
Actrapid	Recombinant DNA	30 mins	2.5-5 hours	8 hours
Humulin R	Recombinant DNA	20-30 mins	1-3 hours	5-7 hours
Intermediate-acting				
Protophane	Recombinant DNA	90 mins	4-12 hours	18-24 hours
Humulin N	Recombinant DNA	60 mins	2-8 hours	18-20 hours
Long-acting				
Glargine (Lantus)	Recombinant DNA	1-2 hours	No peak	20-24 hours
Detemir (Levemir)	Recombinant DNA	30-60 mins	No peak	20-24 hours
Pre-mixed				
Humulin 30/70	Recombinant DNA	30 mins	1-8 hours	14-15 hours
Actraphane	Recombinant DNA	30 mins	2-12 hours	16-24 hours
Humalog Mix 75/25	Recombinant DNA	5-15 mins	Dual	10-16 hours
NovoLog Mix	Recombinant DNA	5-15 mins	Dual	10-16 hours

logues differ from conventional insulin in their pharmokinetic profiles. All insulin analogues approved for clinical use are comparable to conventional insulins with respect to their safety profiles and ability to induce antibody production.

Rapid-acting

Manipulation of amino acids in the β-chain of insulin has resulted in the development of three ultra-short-acting insulin analogues, namely insulin lispro (Humalog, Eli Lilly), insulin aspart (NovoRapid, Novo Nordisk) and insulin glulisine (Apidra, Sanofi Aventis). Insulin lispro was developed by the reversal of amino acids proline (position 28) and lysine (position 29); insulin aspart was formed by the substitution of proline (position B28) with aspartic acid; and insulin glulisine was developed by substitution of asparagine (position 3) with lysine and lysine (position 29) with glutamic acid. These alterations have resulted in insulin molecules with a decreased ability to self-associate, thereby increasing the absorption rate. As a consequence, the onset of action is more rapid and the duration of action is reduced (see Figure 1 C). Regimens using rapid-acting analogues have been shown to induce a small but significant reduction in HbA1c and comparable results in overall hypoglycemia when compared to regimens using regular insulin.[2,3] The use of these analogues was shown to improve quality of life, largely due to the shorter interval between insulin administration and eating. In children they offer the option of being given after meals, particularly in toddlers who are reluctant to eat. Of note is that there currently is no long-term efficacy and safety data for the use of these agents and therefore they should be used cautiously.[2]

Long-acting

In an attempt to develop an insulin that can best provide a 24-hour predictable and stable basal level without peaks and troughs, recombinant DNA techniques have been used to develop insulin glargine (Lantus, Sanofi Aventis) and insulin detemir (Levemir, Novo Nordisk). Studies comparing the use of these agents with NPH insulin have shown no significant improvement in HbA1c, but some studies have shown a reduction in hypoglycaemic events (especially nocturnal hypoglycaemia).[4,5,6] The results of studies in children and adolescents using long-acting insulin analogues are comparable to those of adults.[7]

Insulin glargine: This analogue was formed by the addition of two arginine residues to the C-terminal end of the β-chain of insulin, as well as the substitution of asparagine (position 21 of the -chain) with glycine. This insulin molecule is less soluble at physiological pH levels and therefore precipitates once injected into the subcutaneous tissues. This delays absorption and increases the duration of action. The net clinical effect is a single daily injection that provides a glucose-lowering effect for 24 hours without a pronounced plasma peak (see Figure 1 D).

Insulin detemir: The addition of a fatty acid to the insulin molecule enables binding to albumin. As albumin has a slow disappearance rate from the subcutaneous tissues, there is a delay in the absorption of this insulin molecule, thereby prolonging its duration of action.

INSULIN REGIMENS

There is convincing evidence that decreasing the HbA1c to < 7% in patients with type 1 diabetes mellitus prevents or delays the onset of microvascular (retinopathy, neuropathy, nephropathy) complications.[8,9,10,11] Furthermore, any decrease in the HbA1c concentration is associated with a decline in the relative risk of microvascular complications. The DCCT/EDIC cohort has shown that a period of good glycaemic control can reduce long-term macrovascular disease.[12] Thus, the clinician should strive to decrease the HbA1c, targeting a value of < 7% but bearing in mind that any decrease in the HbA1c translates into a decreased risk of complications. Unfortunately, as the HbA1c decreases towards the target value, the risk of hypoglycaemic episodes increases. This necessitates that the treating clinician choose a therapeutic regimen that realises the target HbA1c with minimal hypoglycaemic episodes. Insulin therapy is the mainstay of treatment, with various types of insulin and insulin dosing regimens from which to choose. The array of choice often creates uncertainty amongst clinicians, but the following basic principles are suggested:

1) Individualise therapy
2) Start with the simplest regimen with which your patient will be compliant
3) Aim for an HbA1c under 7% (in some cases this may not be achievable, as significant hypoglycaemic episodes may occur when approaching this target)
4) "Start low and go slow", avoiding hypoglycaemic episodes that are dangerous and serve to undermine the confidence of your patient with the specific insulin regimen
5) Regular glucose monitoring is essential (rule of thumb: patients should check their blood glucose before every insulin injection)

Prior to commencing insulin therapy, it is advisable that children be assessed by a specialist paediatrician or at a centre dedicated to managing children with diabetes mellitus.

1) Basal bolus regimen

Rationale: strives to mimic normal physiology by providing a rapid-acting insulin prior to each meal, thereby reducing postprandial glucose peaks, and an intermediate to long-acting insulin at night to provide a basal insulin level.

Regimen:

Rapid-acting insulin

Given at time-point A (Figure 1 A) before breakfast, lunch and supper.

- Public sector – usually only have access to rapid-acting regular human insulin (Actrapid and/or Humulin R). This insulin should be given 30 minutes prior to meals.
- Private sector – access to rapid-acting regular human insulin as well as the insulin analogues (insulin lispro, insulin aspart and insulin glulisine). These can be given 10 to 15 minutes prior to a meal or with a meal. Since these have a more rapid onset of action, their peak effect coincides with the postprandial glucose peak, thereby decreasing postprandial hypoglycaemic episodes. To children they are usually given with a meal and sometimes afterwards, especially to toddlers.

Intermediate / long-acting insulin

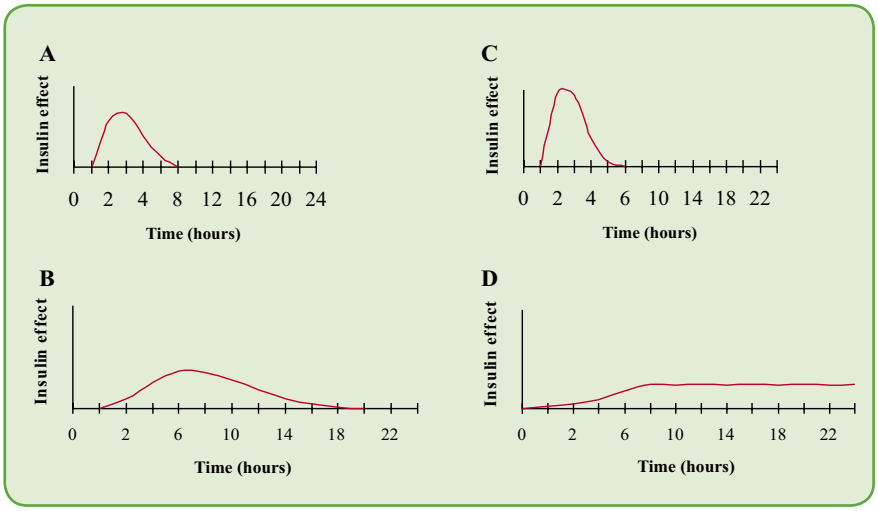
Given at time point B (Figure 1 A) at 22h00.

- Public sector – Protophane and/or Humulin N
- Private sector – Protophane, Humulin N, insulin glargine (Lantus), insulin detemir (Levemir)

This insulin dose provides a basal level over 18 to 24 hours. Since there is a significant amount of insulin present at a time when the patient is sleeping and not eating, a pre-sleep snack is important to decrease nocturnal hypoglycaemia. Lantus and detemir do not have a peak and provide a "smoother" insulin profile, thereby decreasing hypoglycaemic episodes, especially those that occur at night.

A snack should be eaten before sleep to prevent potential hypoglycaemia that occurs when the intermediate-acting insulin is peaking in the early hours of the morning (time-point C, Figure 2).

Figure 1: A rapid-acting regular (soluble) insulin, **B** NPH insulin, **C** rapid-acting insulin analogues, **D** long-acting insulin analogues



Starting dose:

Adults

units of insulin/day = 0.3 x body weight (kg)
60% given as rapid-acting insulin
40% given as intermediate to long-acting insulin

Children

units of insulin/day = 0.6 x body weight (kg)
50-70% given as rapid-acting insulin
30-50% given as intermediate to long-acting insulin

Prepubertal children usually require 0.6-1.0 u insulin/kg/day, but during puberty the insulin requirements may rise substantially above 1.0 u/kg/day.[13]

Patients should monitor their blood glucose prior to each insulin dose and can be taught to adjust their insulin dosage according to their blood glucose reading, thereby decreasing risks of hyperglycaemia and hypoglycaemia.

Which patient?

This regimen requires multiple blood glucose monitoring and multiple injections daily and will best suit a patient that is motivated, has insight into their illness, can tolerate multiple needle-sticks, and is able to carry their glucometer and insulin with them during the day. An added advantage with this regimen is that the insulin dose can be omitted if a meal is to be missed, although all diabetics should strive to eat regular meals.

2) Bi-daily regimen

Rationale: Premixed insulin containing a rapid-acting insulin and an intermediate to long-acting insulin. This mixture is given before breakfast and before supper. The rapid-acting insulin serves to decrease the postprandial glucose peak occurring after breakfast and supper, whilst the intermediate to long-acting insulin provides a basal level.

Regimen:

Premixed insulin

Given at time points A (Figure 3) 30 minutes before breakfast and supper

- Public sector - Actraphane and Humulin 30/70
- Private sector - Actraphane, Humulin 30/70, Humalog Mix25 and NovoMix 30

Snacks should be eaten at time points B (see Figure 3) to prevent daytime hypoglycaemic episodes, as the insulin levels are still high relative to the postprandial serum blood glucose level at those time points. An additional snack should be taken before sleep (time point C, Figure 3) to prevent potential hypoglycaemia that occurs when the intermediate-acting insulin is peaking in the early hours of the morning (time point D, Figure 3).

Starting dose:

Adults

units of insulin / day = 0.3 x body weight (kg)
66% of dose given before breakfast
33% of dose given before supper

Children

units of insulin / day = 0.6 x body weight (kg)
66% of dose given before breakfast
33% of dose given before supper
This dose will be adjusted according to weight and pubertal stage, as indicated previously.

Which patient?

This regimen is more applicable to the patient who is less motivated, cannot tolerate multiple needle-sticks and will not have access to their glucometer and insulin during the day. An additional disadvantage of this regimen is the necessity to have regular snacks at mid-morning, mid-afternoon and mid-evening, to decrease the likelihood of hypoglycaemic episodes.

3) Three-times-a-day regimen

Rationale: If the insulin given with supper in the bi-daily regimen does not last until morning, then the rapid-acting component should be given before supper and the intermediate to long-acting component should be postponed until just before bedtime. This is particularly useful in children, as it decreases the risk of nocturnal hypoglycaemia and the dawn phenomenon (hyperglycaemia prior to awakening).

Figure 2: Basal bolus insulin regimen

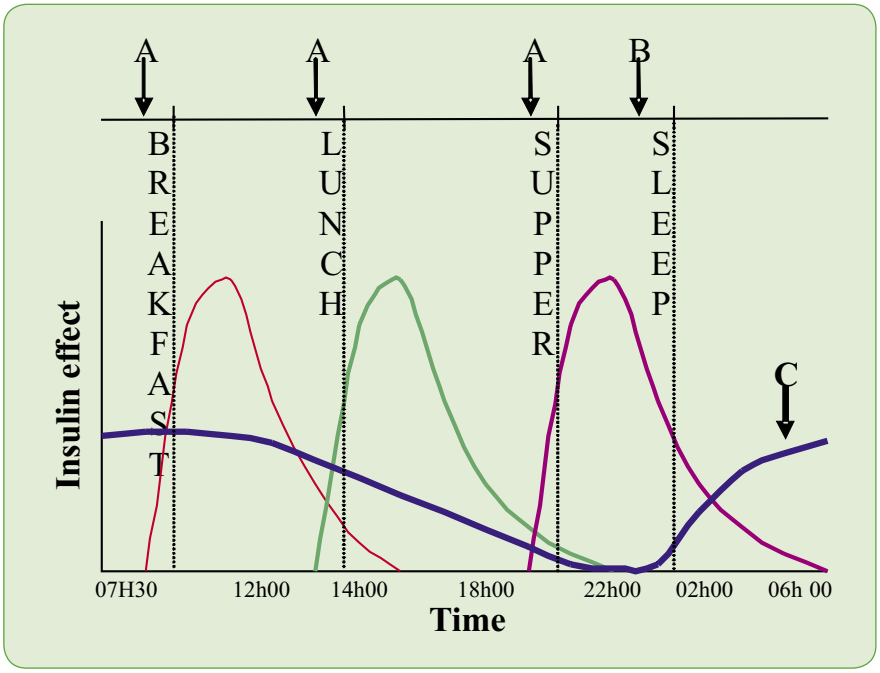
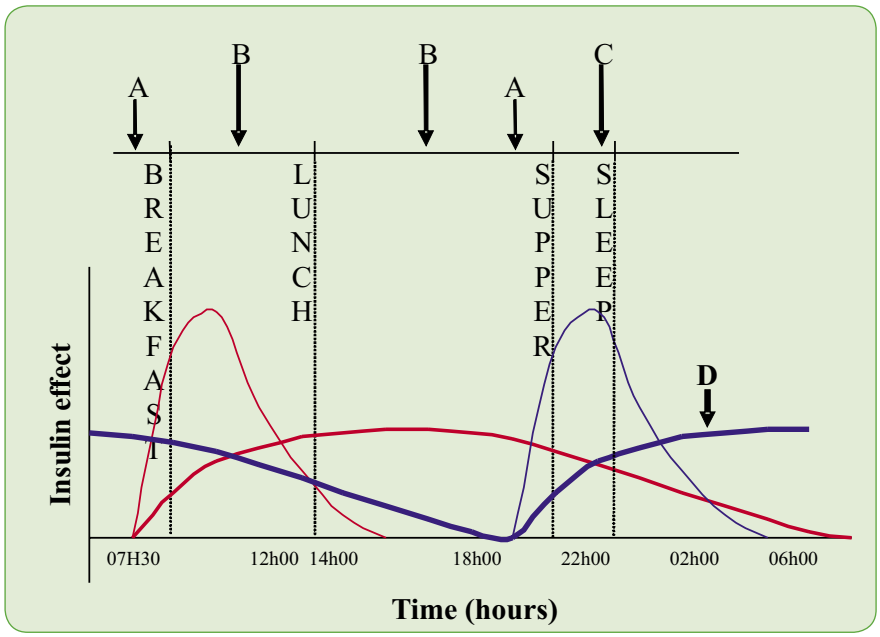


Figure 3: Bi-daily insulin regimen



Regimen:

Premixed insulin (see bi-daily regimen)

Given at time point A (Figure 4) 30 minutes before breakfast.

The rapid-acting and intermediate-acting insulins can be also be given individually to individualise doses.

Rapid-acting insulin (see basal bolus regimen)

Given at time point B (Figure 4) before supper.

Intermediate / long-acting insulin (see basal bolus regimen)

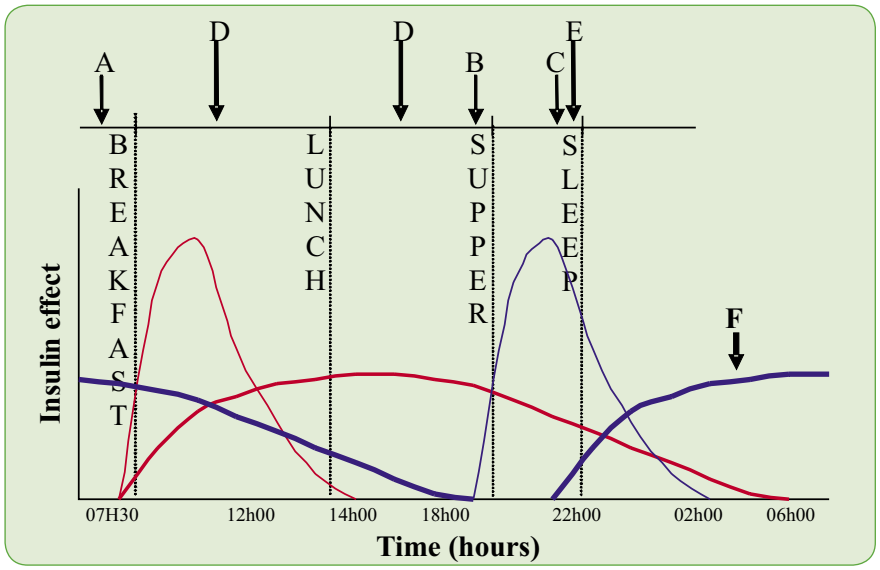
Given at time point C (Figure 4) at 21h00 to 22h00.

Snacks should be eaten at time points D to prevent daytime hypoglycaemic episodes, as the insulin levels are still high relative to the postprandial serum blood glucose level at those time points. An additional snack should be taken before sleep (time point E, Figure 4) to prevent potential hypoglycaemia that occurs when the intermediate-acting insulin is peaking in the early hours of the morning (time point F, Figure 4).

4) Insulin infusion pump

This is probably the gold standard form of therapy, but it is expensive and beyond the affordability of the majority of patients. The rationale for its use is similar to that of the basal bolus regimen. Using the pump, patients receive a continuous basal level of insulin and a bolus dose prior to each meal. The boluses can be programmed or performed manually.

Figure 4: Three-times-a-day regimen



CONCLUSION

The suggested insulin regimens are a safe way to initiate insulin treatment, but no insulin regimen satisfactorily mimics the normal physiology and no regimen can be optimised without individualising therapy and frequent assessment through blood glucose monitoring.

USEFUL INTERNET WEBSITES

- International Society for Pediatric and Adolescent Diabetes (ISPAD) (www.ispad.org)
- ISPAD consensus guidelines for the management of type 1 diabetes in children and adolescents (www.ispad.org)
- American Diabetes Association (www.diabetes.org/home.jsp)
- South African National Diabetes Guidelines (www.semdsa.org.za)
- Patient information (www.diabetes.niddk.nih.gov/)
- Patient information (www.diabetes.com)

See CPD Questionnaire, page 48

This article has been peer reviewed

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