INSULIN Therapy Made Easy

Editor
Sanjay Kalra

Co-Editor
Binayak Sinha

Foreword
AK Das

JAYPEE

Contents

CHAPTER 2

Profile of Insulins

Binayak Sinha

INTRODUCTION

In a healthy individual, rapid insulin releases from pancreatic β-cells of Langerhans is observed after ingestion of meal. Post a mixed meal, endogenous insulin level is observed to reach half of the maximum concentration in the blood within 16–18 minutes and reaches peak level within 35–40 minutes. As a result, there is moderate postprandial glycemic excursion (PPG) after heavy carbohydrate intake. This insulin regulation system is disrupted in patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM).[1]

Based on the source, insulins are classified as natural animal insulin, recombinant human insulin, and insulin analogs.[2] Based on the onset and duration of action, insulins are further classified into different categories namely, short-/rapid-acting, intermediate-acting, long-acting, ultra-long acting, and premix (dual-action) insulins (**Table 1**).[3] Recently, co-formulation of two different insulins has also been made available [e.g., insulin degludec/insulin aspart (IDegAsp)].[4]

Regular human insulin, developed in 1982, was the first genetically engineered drug to be approved by the US Food and Drug Administration (FDA).[5] It was produced by inserting insulin-producing human genes into *Escherichia coli* bacteria, thereby stimulating the bacteria to synthesize insulin.[6] Regular human insulin was the mainstay of insulin therapy until the advent of insulin analogs.[7]

In 1996, introduction of insulin analogs as insulin therapy has proved to be a good treatment option for T1DM and T2DM. New generation insulin therapies are now capable of mimicking physiological insulin secretion and are helping to achieve better glycemic control without compromising on the safety.[8]

Insulin analogs are developed by altering amino acid (AA) sequence and/or minor structural change done with the help of recombinant DNA technology. Such alterations lead to desirable absorption, distribution, metabolism, and excretion of the new molecule. Once absorbed, these insulin analogs mimic the action of endogenous insulin.[9] Commercially, variety of insulin analogs are available, and a thorough understanding of their pharmacokinetics (PK) and pharmacodynamics (PD) properties is essential for achieving good glycemic targets in a safe and well-tolerated manner.[10]

The different types of insulin, their structural changes, mechanism of action, advantages, and limitations are explained in this chapter.

TABLE 1 **Types of insulin based on duration.**

Type of insulin		Description	Insulin analog*
Prandial Insulin	• Short-/rapid-acting insulin	• Soluble insulins usually taken before meals • Help control PPG levels	• Short acting–RHI • Rapid acting–IAsp, ILis, IGlu
	• Ultrafast acting insulin	• Improved time-action profile due to faster absorption	• Fast-acting insulin aspart
Basal Insulin	• Intermediate-acting insulin	• Rendered insoluble by combination with protamine, which slows absorption from the subcutaneous tissue and extends the duration of insulin	• NPH
	• Long-acting insulin	• Absorbed slowly, duration of action ≤24 h • Provide basal coverage to control the blood glucose levels overnight, while fasting, and between meals	• IGlar U100, IDet
	• Ultralong-acting insulin	• Absorbed very slowly, have no peak effect with ultra-long duration of action of >24 h • Provide basal coverage to control the blood glucose levels overnight, while fasting and between meals, through single daily injection with flexibility	• IDeg, IGlar U300
Premixed insulins	• High-mix insulin	• Contain high ratio of short-/rapid-acting to intermediate-/long-acting insulin analog as bolus and basal components in the same preparation	• BIAsp 50/50, LisproMix 50/50 and BHI 50/50
	• Low-mix insulin	• Contain low ratio of short-/rapid-acting to intermediate-/long-acting insulin analog as bolus and basal components in the same preparation	• BIAsp 30/70, LisproMix 25/75 and BHI 30/70
Co-formulation		• Both rapid and ultralong-acting insulins as bolus and basal components in the same preparation • May also include GLP-1 RA combined with a basal insulin	• IDegAsp (70/30), IDegLira, IGlarLixi

(GLP-1 RA: glucagon-like peptide-1 receptor agonist; IAsp: insulin aspart; IDeg: insulin degludec; IDegAsp: insulin degludec/insulin aspart; IDegLira: insulin degludec/liraglutide; IDet: insulin detemir; IGlar: insulin glargine; IGlarLixi: insulin glargine/lixisenatide; IGlu: insulin glulisine; ILis: insulin lispro; NPH: neutral protamine Hagedorn; PPG: postprandial glucose)

Adapted from: Reference no. 1, 11, 12.

SHORT AND RAPID-ACTING INSULINS

General Description and Time Action Profile

Insulin analogs are developed by minor changes in structure or AA sequence (by recombinant DNA technology), which provide desirable absorption, distribution, metabolism, and excretion. Once absorbed, these insulin analogs mimic the action of endogenous insulin.[11] Regular human insulin/rapid-acting insulin analogs are an aggregate of six molecules, i.e., hexamers. After subcutaneous injections, hexamers break up slowly into dimers and monomers, and are finally absorbed and circulated in the bloodstream.[2]

Regular human insulin is short-acting soluble insulin. It has an AA composition indistinguishable from endogenous insulin.[13] It appears as a clear solution which can be administered subcutaneously, intramuscularly, or intravenously.[14] The dissociation from hexamers to dimers/monomers results in 30–60 minutes delay in its onset of action.[8] The limitations of regular human insulin include:

- Variable absorption
- Delayed onset of action and a late peak after subcutaneous injection. This limits its flexibility and convenience of time of administration as it should be injected 30 minutes before the meals.
- Prolonged duration of action with a slow decline after the peak is reached, this may lead to higher risk of late postprandial hypoglycemia.[15]

Rapid-acting insulin analogs are designed to offer more rapid onset of action and shorter duration of activity than normal human soluble insulin. Currently, insulin aspart (IAsp), insulin lispro (ILis), and insulin glulisine (IGlu) are three commercially-available rapid-acting insulin analogs.[11,16] Alteration in AA sequence prevents self-association into dimers and hexamers thus, leading to faster absorption in the blood along with a rapid onset of insulin action.[11,16,17] This helps in higher treatment flexibility, less risk of postprandial and nocturnal hypoglycemia, decreased glycemic variability across the day, consistent PK profile across all age ranges, and superior blood glucose control.[18] Rapid-acting insulin analogs exhibit better postprandial glucose control when compared to human insulin due to closer PK/PD profile similarity with the mealtime endogenous insulin secretion.[19-22]

Rapid-acting insulin analogs are ideal for prandial insulin replacement and should be injected at mealtimes for high blood glucose correction.[23] Rapid-acting analogs can be administered just before meals or immediately after the meals as these analogs rapidly enter the bloodstream following subcutaneous injection.[18] The peak action period is 60–120 minutes with a shorter duration of action (3-5 h) (**Figs. 1** and **2**). Doses are usually adjusted to match anticipated carbohydrate intake. Generally, injection of rapid-acting analogs results in twice the maximal concentration and takes half the amount of time to reach maximal concentration as compared to equivalent doses of regular human insulin.[24]

Rapid-acting insulin analogs are approved for use in insulin pumps [continuous subcutaneous insulin infusions (CSII) devices] and in form of vials and syringes and insulin pens.[25] The advantages of rapid-acting insulin analogs against human regular insulin are summarized in **Table 2**.

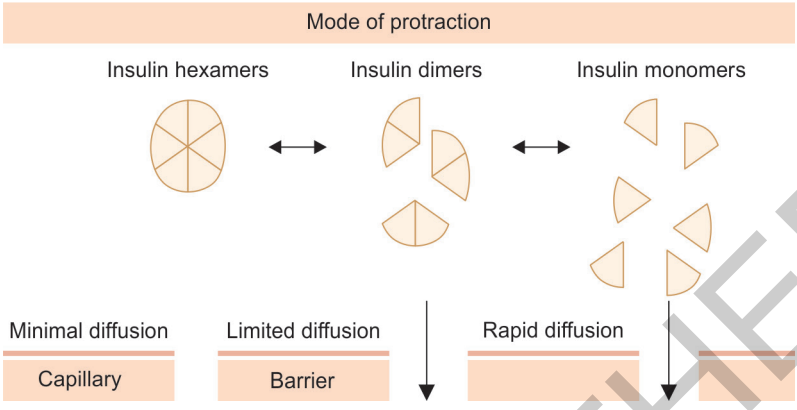


FIG. 1: Mode of protraction.
Adapted from: Reference no. 24.

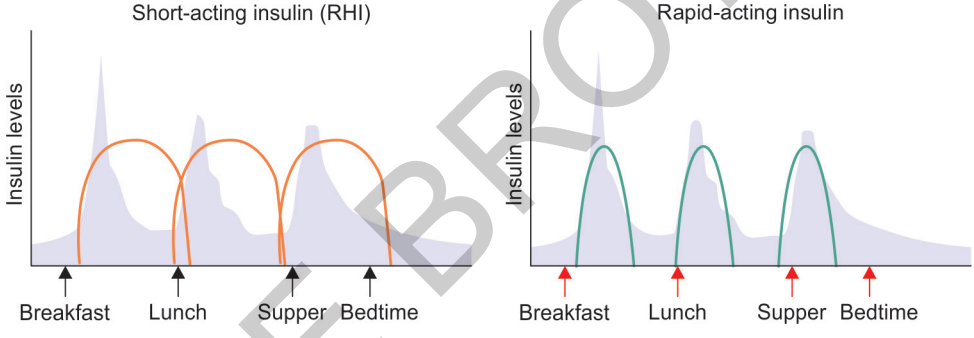


FIG. 2: Time action profile: Short-acting and rapid-acting insulins.
Adapted from: Reference no. 24.

TABLE 2 **Advantages of rapid-acting insulin analogs against regular human insulin.**

PK/PD benefits	Clinical benefits
Rapid onset of action	Offers flexibility and can be taken immediately before a meal
Similar PK/PD characteristics across age groups	Convenient for very young children and older people with variable food intake, leading to greater adherence and flexibility with prescribed injection timings (higher compliance and treatment satisfaction)
Consistent pharmacokinetics	Less day-to-day variability in absorption rates between and within patients
Higher C_{max} for insulin concentration	Improved postprandial glycemic control and HbA1c control
Shorter duration of action	Reduced risk for late postprandial and nocturnal hypoglycemia

(C_{max}: maximum serum insulin concentration; HbA1c: glycosylated hemoglobin; PD: pharmacodynamics; PK: pharmacokinetics)
Adapted from: Reference no. 15, 26.

Individual Pharmacological Profile

Regular Human Insulin

As discussed in above, regular human insulin exhibits delayed absorption and delayed peak effect and long duration of action (7-8 h), whereas plasma glucose levels usually rise more quickly after meals.[27,28] Such inconsistency (insulin and plasma glucose level) creates a brief hyperglycemic period immediately after the meal and a potential hypoglycemic period 3–4 hour post meal.[23]

Rapid-acting Insulin Analogs (IAsp, ILis, and IGlu)

Rapid-acting insulin analogs are rapidly absorbed in <15 minutes following subcutaneous injection, have a short time to peak concentration (0.5–3 h), and shorter duration of action (3–5 h) as compared with regular human insulin (**Table 3**).[20]

Insulin Aspart

Insulin aspart has a single substitution of the AA proline by aspartic acid at position B28 of the β-chain of insulin, resulting in faster dissociation of hexamers into monomers resulting in a faster absorption profile.[29] It is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* and was approved in the year 2000.[30] It has an onset of action of 10–15 minutes, reaches maximum serum concentration at 30–90 minutes, and the duration of action is 3–5 hours. The maximum glucose-lowering effect occurs between 1 and 3 hours, following subcutaneous injection.[8] Various studies have shown IAsp to be effective in patients with T1DM and T2DM and offer better PPG control than regular human insulin. Overall and nocturnal hypoglycemia is also lower with IAsp than regular human insulin.[31]

Ultra-fast Acting Insulin Analog: Fast-acting Insulin Aspart

Fast-acting IAsp was approved in 2017. Two excipients were added to the formulation of IAsp, i.e., niacinamide to increase the speed of absorption, and L-arginine

TABLE 3 Pharmacology of prandial insulins.

Type of insulin	Onset (min)	Peak (h)	Duration (h)
Short-acting insulin			
Regular insulin	~30	1.5–3.5	7–8
Rapid-acting insulin			
Insulin aspart	<15	~1	3–5
Insulin lispro	<15	~1	3–5
Insulin glulisine	<15	~1	3–5
Ultra-fast acting insulin			
Fast-acting insulin aspart	4.9 min earlier than insulin aspart	7 min earlier than insulin aspart	Shorter than insulin aspart, ~3–5

Onset is defined as how quickly the insulin acts; Peak is defined as how long it takes to achieve maximum effect; Duration is defined as how long the insulin action will last before it fades off.

Adapted from: Reference no. 8.

for stability.[31] Fast-acting IAsp is absorbed faster than IAsp.[24] It results in earlier occurrence of insulin in the blood (by 5 min), and has a faster glucose-lowering effect (74% greater) within the first 30 minutes after injection and an early offset of action by 12–14 minutes as compared to IAsp.[32] It is noninferior to conventional IAsp for glycemic control and offers significantly better postprandial glucose levels and improve glycosylated hemoglobin (HbA1c) along with basal insulin.[33-35]

Insulin Lispro

Insulin lispro was the first available rapid-acting insulin analog that was approved in 1996.[36,37] It has been produced by recombinant DNA technology utilizing a nonpathogenic strain of *E. coli*. The name "lispro" has originated from two AAs—lysine and proline, the position of both of which are reversed at B28 and B29, respectively on β-chain of insulin.[38] This results in a lower tendency to self-aggregate into dimers and hexamers. The onset of action is within 15 minutes, and the duration of action is 3–5 hours.[8,39]

Published literature suggests a greater reduction in PPG levels and lower risk of hypoglycemic episode with ILis compared to regular human insulin in patients with T1DM and T2DM.[38-40]

Insulin lispro 200 U/mL is a variant of ILis 100 and contains same number of units in half the volume. The major differences between the two include change of strength from 100 to 200 U/mL, increased zinc ion concentration, and changed buffer agent (trometamol instead of phosphate buffer). However, tolerability, efficacy, and PK/PD responses are similar for both the formulations. ILis 200 U/mL is mostly used in patients with diabetes requiring higher daily mealtime insulin doses, thereby allowing the patients to change insulin pens less frequently.[41]

Insulin Glulisine

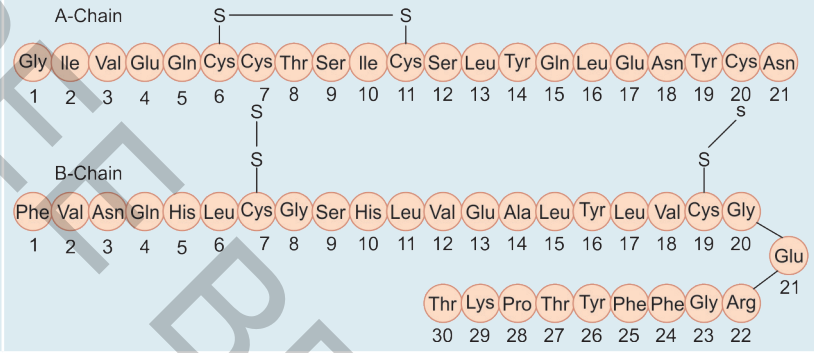
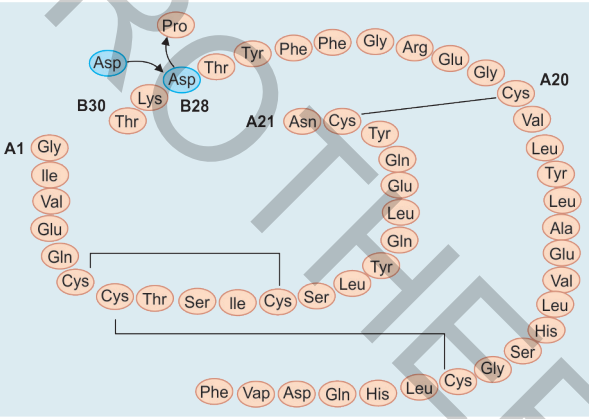
insulin glulisine, approved by FDA in 2004, is produced by recombinant DNA technology utilizing a nonpathogenic strain of *E. coli* (K12). It differs from human insulin in that the AA (glutamic acid) is exchanged for lysine at position B29 and lysine for asparagine at position B3 of insulin β-chain.[42] It has shown more rapid absorption than that of regular human insulin and does not require additional zinc to stabilize the preparation.[43] The onset of action is within 15 minutes, and the duration of action is 3–5 hours.[8] IGlu, with and without basal insulin, has been found to be effective in terms of lowering glucose levels in patients with T1DM and T2DM.[44,45]

The structures of all rapid-acting insulin analogs are presented in **Table 4**.

Usage of Short-, Rapid- and Ultrafast-acting Insulins in Special Population

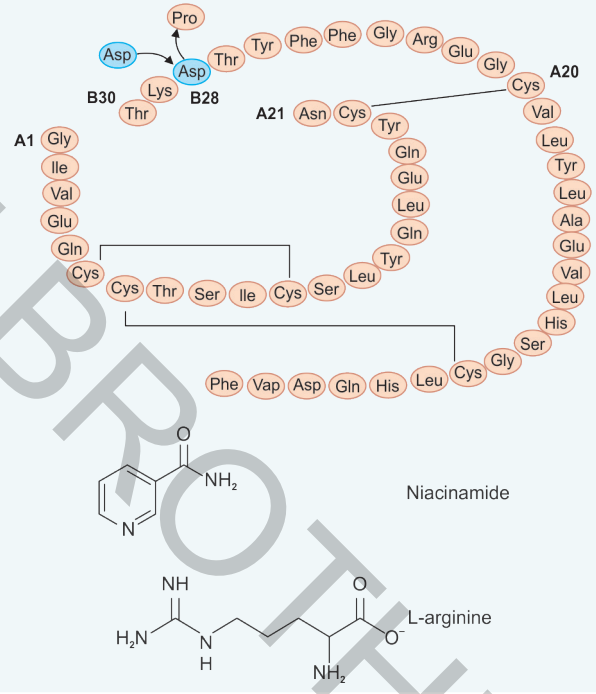
Intravenous (IV) insulin therapy is recommended over subcutaneous therapy in critically ill patients with or without diabetes (**Table 5**).[47] They should be used at concentrations 0.05–1 units/mL in infusion systems; under strict medical supervision with close monitoring of blood glucose and potassium levels.[20,27] Fast-acting IAsp, IAsp, ILis, and IGlu, are compatible with 0.9% sodium chloride for IV use. However, only IGlu is not compatible with dextrose and Ringer's lactate solution.[11]

TABLE 4 Structure of short and rapid-acting insulins.

Insulin	Structural change	Structure
Human insulin		
Regular human insulin	Polypeptide hormone containing 2 AA chains: A chain containing 21 AA and B chain containing 30 AA	
Insulin analogs		
Insulin aspart	Replacement of proline at B28 with aspartic acid	

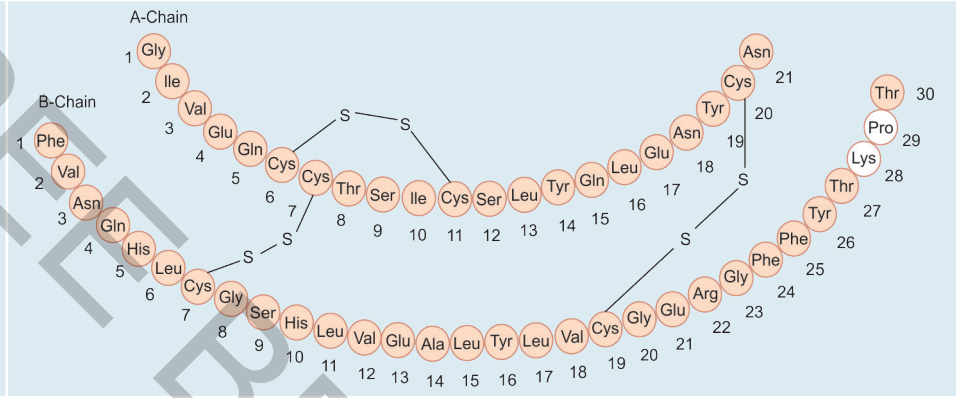
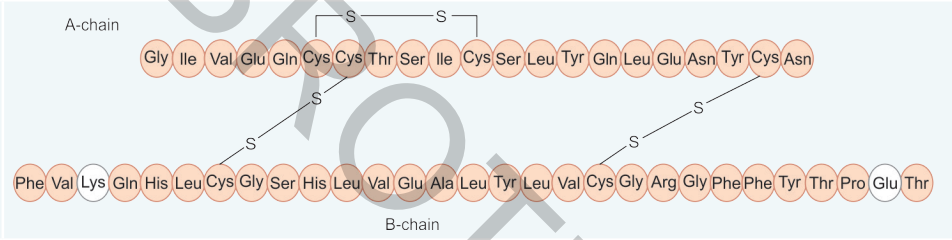
Continued

Continued

Insulin	Structural change	Structure
Fast-acting insulin aspart	• Replacement of proline at B28 with aspartic acid • Addition of niacinamide and L-arginine	

Continued

Continued

Insulin	Structural change	Structure
Insulin lispro U100 and U200	Reversal of lysine and Proline at B28 and B29	
Insulin glulisine	Replacement of Asparagine at B3 with lysine and lysine at B29 by glutamic acid	

Adapted from: Reference no. 46.

TABLE 5 Use of short- and rapid-acting insulin in special population.

Type of insulin	Pediatric	CKD	CLD	Pregnancy	IV use	IV fluid compatibility	Insulin pumps
Regular insulin[48]	Can be used	Dose reduction recommended	Dose reduction recommended	Approved, FDA Category B • EMA: Can be used • Indian label: Can be used	IV use	Compatible: Dextrose solution, normal saline, and Ringer's lactate solution	NA
Insulin aspart[49]	≥1 year	Requires more frequent blood glucose monitoring and dose adjustments to be done on individual basis	No effect on PK properties	Approved, FDA Category B • EMA: Can be used • Indian label: Can be used	IV use	Compatible: Dextrose solution, normal saline, and Ringer's lactate solution	Discard insulin after 6 days of insulin pump usage
Fast-acting insulin aspart[50]	≥18 years	Requires more frequent blood glucose monitoring and dose adjustments to be done on individual basis	Absorption rate was decreased and more variable	Approved, FDA: No data • EMA: Can be used • Indian label: Can be used	IV use	Compatible: Dextrose solution, normal saline, and Ringer's lactate solution	Discard insulin after maximum 6 days of insulin pump usage
Insulin lispro U100[37]	≥4 years	Dose adjustments in moderate and severe renal disease as clearance of insulin lispro is reduced	Not studied	Approved, FDA Category B • EMA: Can be used • Indian label: Can be used	IV use	Compatible: Dextrose solution, normal saline, and Ringer's lactate solution	Discard insulin after 7 days of insulin pump usage
Insulin glulisine[51]	≥4 years	Frequent glucose monitoring and insulin dose reduction may be required	Increased circulating levels of insulin in patients with liver failure	• No targeted trials • FDA Category C • EMA: No data • Indian label: No data	IV use	• Compatible: 0.9% sodium chloride • Incompatible: Dextrose solution and Ringer's lactate solution	Discard insulin after 2 days of insulin pump usage

(CKD: chronic kidney disease; CLD: chronic liver disease; EMA: European Medicines Agency; FDA: Food and Drug Administration; IV: Intravenous; PK: pharmacokinetics)

INTERMEDIATE AND LONG-ACTING INSULINS

General Description and Time Action Profile

The duration of regular human insulin can be extended by the addition of protamine (strong basic proteins extracted from the nucleus of fish sperm) at neutral pH to form isophane or neutral protamine Hagedorn (NPH) insulin (intermediate-acting insulin). Protamine, after binding with insulin, reduces its solubility after injection, and further delays the absorption.[8] Addition of excess zinc ions crystallizes insulin, enhances its aggregation into dimers and hexamers, and delays the release following subcutaneous injection, e.g., protamine zinc insulin (PZI), which is insulin combined with zinc and protamine.[52]

The long-acting analogs help to control fasting plasma glucose (FPG) levels. They are used along with prandial insulin as basal-bolus therapy in patients with T1DM and as basal insulin regimen in combination therapy with oral antidiabetics (OADs), noninsulin injectable therapies, and/or prandial insulins in patients with T2DM.[28,53] The advantages of long-acting insulin analogs compared to NPH are as follows:

- *Basic pharmacology*:
  - Have changes in the AA sequence, which makes insulin less soluble at physiological pH and delays its absorption.
  - Relatively flat, and protracted basal insulin levels.
  - Longer duration of action.
- *Clinical implications*:
  - Lesser interpatient and intrapatient day-to-day variability.
  - More predictability.
  - Lesser risk of hypoglycemia.

Individual Pharmacological Profile

Tables 6 and **7** summarize the profile and pharmacology of intermediate and long-acting insulin analogs and usage in special populations.

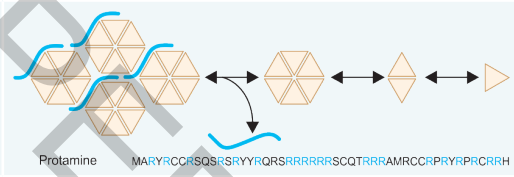
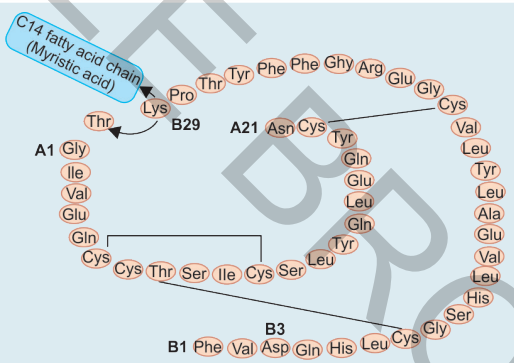
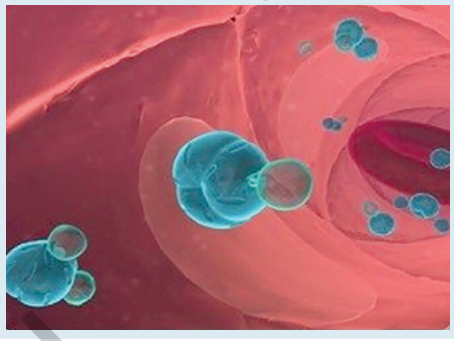
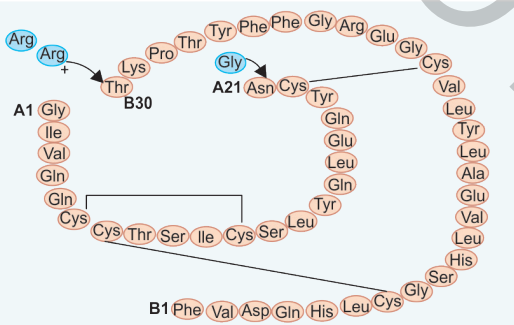
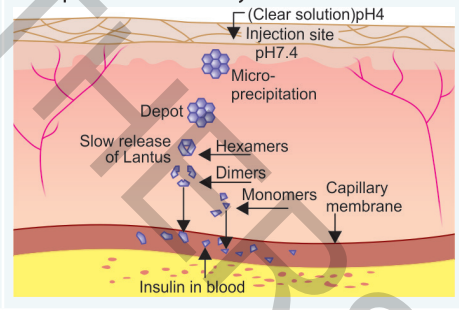
Neutral Protamine Hagedorn

Neutral protamine Hagedorn or isophane insulin is a crystalline suspension, which enhances aggregation into dimers and hexamers after subcutaneous injection.[43] This decreases the onset of action and also provides a longer duration of action than the short and rapid-acting insulins.[8,54] NPH insulin displays a peak in its action at around 4–10 hours after subcutaneous injection and the duration of action is close to 24 hours.[55] However, due to its side-effects, its use has been limited and has led to the development of long-acting basal insulin analogs which yield better action profiles as seen with IDeg (**Fig. 3**).[56]

Following are the limitations of the conventional intermediate-acting insulins:[57]

- Variable absorption
- Peak between 4 and 10 hours from injection
- Variable duration of action (10–20 h).
- May require two injections/day.

TABLE 6 Types of intermediate- and long-acting insulin.

Type of insulin	Structural change	Structure	Mechanism of protraction
Neutral protamine Hagedorn (NPH)[8,88]	Protamine (an arginine rich protein) added to regular human insulin		Decreased solubility at physiological pH due to basic nature of protamine
Insulin detemir[89]	Fatty acid (myristic acid) is bound to lysine AA at position B29 and with removal of threonine from B30		Extensive albumin binding 
Insulin glargine U100[90]	Substitution of glycine for asparagine at A21 and two arginine residues added to the carboxy terminal of B chain		Precipitates as microcrystals 

Continued

INSULIN Therapy
Made Easy

Insulin is a faithful friend, provided we understand the basic science that supports its use. This book describes the basic and clinical pharmacology of insulin, and explains the practical aspects of insulin use. The reader-friendly format of this book makes insulin therapy easy to prescribe and easy to use.

Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
ENDOCRINOLOGY