Use of Insulin in treatment of diabetes mellitus

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@@= introduction
green-= notes
$ $ = not imp

imp. Notes
At The End

Objectives:

by the end of this lecture, students should be able to:

- *Define diabetes and mention different types of diabetes*
- *Differentiate between difference in treating type I and type II diabetes.*
- *Understand mechanism of action, secretion, and actions of insulin.*
- *Describe different types of insulin analogues*
- *Be able to recognize the difference in pharmacokinetic profile between different types of insulin analogues.*
- *Know uses of different insulin analogues*

@@ Diabetes mellitus

- **Is a *chronic* metabolic disorder characterized by high blood glucose level caused by insulin deficiency and sometimes accompanied with insulin resistance.**
- **Fasting plasma glucose > 7 mmol/L (126 mg/dl) is diagnostic of diabetes or**
- **Plasma glucose > 11.1 mmol/L (200 mg/dl), 2h after a meal confirms a diagnosis of diabetes.**

@@ Complications of diabetes

- **Cardiovascular problems**
  - **Microangiopathy**
  - **Macrovascular disease**
- **Renal failure (nephropathy).**
- **Blindness (retinopathy).**
- **Neuropathy (neuropathy).**
- **Risk of foot amputation**

@@ Types of diabetes

- **Type I diabetes**

  due to autoimmune or viral diseases

- **Type II diabetes**

  due to genetic susceptibility and environmental factors (age, obesity)

@@ Type I Diabetes

- **β-cells are destroyed.**
- **absolute deficiency of insulin.**
- **Treated by insulin.**

@@ Type II Diabetes

- **Inadequate insulin secretion (*β-cells are not able to produce appropriate quantity of insulin*).**
- **Insulin resistance in target tissues.**
- **Treated by oral hypoglycemic drugs (either act on Beta- pancreatic cell to produce insulin or decrease insulin resistance).**
- **20-30% of patients may require additional insulin treatment.**

Characteristic	Type 1	Type 2
Onset (Age)	Usually during childhood or puberty	Usually over age 40
Type of onset	Abrupt	Gradual
Prevalence	10-20%	80-90 %
Genetic predisposition	Moderate	Very strong
Defects	β-cells are destroyed	β-cells produce inadequate quantity of insulin
Endogenous insulin	Absent	Present (not enough)
Insulin resistance	absent	present
Nutritional status	Usually thin	Usually obese
Ketosis	Frequent	Usually absent
Clinical symptoms	Polydipsia, polyphagia, polyuria, Wt loss	Often asymptomatic
Related lipid abnormalities	Hypercholesterolemia frequent	Cholesterol & triglycerides often elevated
Treatment	Insulin	Oral hypoglycemic drugs

@@ =)

INSULIN

Notes :

•Insulin is Polypeptide so never given by oral route
>> to prevent destruction by gastric secretion.

•Insulin as drug is very safe in pregnancy But
oral Hypoglycemic are not 100 %
Safe.

Insulin receptors

- **Present on cell membranes of most tissues.**
- **Liver, muscle and adipose tissue**

$ $ Effects of insulin *endogenous*

Carbohydrate Metabolism	Fat Metabolism	Protein Metabolism	Potassium
▪↑ glucose uptake & utilization. ▪↑ Glycogen synthesis (glycogen synthase) ▪↑ Conversion of carbohydrate to fats. ▪↓Gluconeogenesis ▪↓ Glycogenolysis (liver). ▪↑ Glycolysis (muscle).	**Liver:** ↑ Lipogenesis. ↓ Lipolysis. Inhibits conversion of fatty acids to keto acids. **Adipose Tissue:** ↑Triglycerides storage. ↑Fatty acids synthesis. ↓Lipolysis	**Liver:** ↓protein catabolism. **Muscle:** ↑amino acids uptake. ↑ protein synthesis. ↑ glycogen synthesis (glycogenesis).	↑ potassium uptake into cells. >>so decrease of insulin leads to hyperkelmeia >>Electrolytes imbalance

Net result: it decreases blood glucose and inhibits all the sources that can give glucose ☺

$ $ Sources of Exogenous Insulin

- **Beef Insulin**
  - **Differs by 3 AA from human insulin (antigenic).**
- **Porcine Insulin**
  - **Differs by one AA (antigenic).**

Old preparations

$ $ Human Insulin.

- **Prepared by recombinant DNA techniques.**
- **Less immunogenic.**
- **Modifications of amino acid sequence of human insulin can change pharmacokinetics.**

(we can have different types of exogenous insulin by change the amino acid sequences, this lead to have different solubility & different rate of absorption)

$ $ Insulin degradation

1. **Basal level of insulin is 5-15 µU/ml.**

endogenous (normal) basal level

2. **Half life of circulating insulin is 3-5 min.**

3. **60% liver & 40% kidney (endogenous insulin)**

→ **because the endogenous insulin is produced by the pancreas then send it through the portal vein which goes to the liver before it enters the circulation**

4. **60% kidney & 40% liver (exogenous insulin) →**

because it is injected directly to the circulation

$ $ Routes of administrations of exogenous insulin :

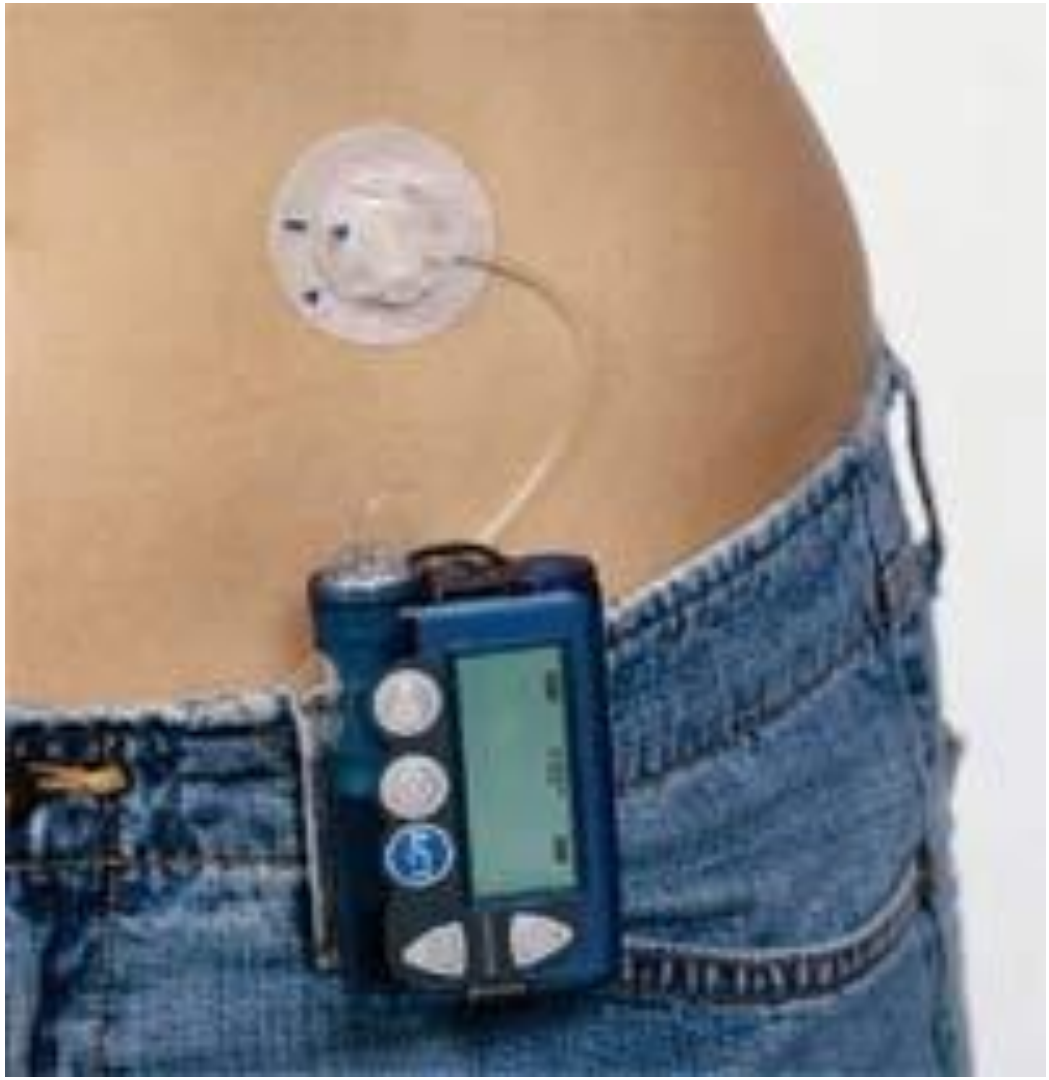
- **Can not be given orally** (why ? B/c it's protein)
- **Insulin syringes (S.C., arms, abdomen, thighs).**
- **Portable pin injector S.C.(pre-filled) .**
- **Continuous S.C. infusion (insulin pump).**
  - **More convenient**
  - **Eliminate multiple daily injection**
  - **Programmed to deliver basal rate of insulin.**
  - More common in diabetic children .
- **Intravenously (in a hyperglycemic emergency like in hyperglycemic Ketoacidosis)**

Under Clinical Trials (still not recommended)

- **Inhaled aerosols, transdermal, intranasal.**

Pin injector

Insulin pump



$ $ Types of insulin preparations

(this slide explains why the insulin preparations are different)

Differs in *pharmacokinetic properties* mainly

- **Rate of absorption**
- **Onset of action**
- **Duration of action.**

(if it's monomer the Rate of absorption is high so onset of action is rapid
But if the drug is hexamer the absorption rate is low so
onset of action delayed and duration of action is prolonged)

Variation is due to

- **Change of amino acid sequence.**
- **Size and composition of insulin crystals in preparations.**

Types of insulin preparations Insulin Analogues

	Ultra-short acting insulins *very fast*	Short acting insulins fast	Intermediate acting	Long acting
Characteristic	•very fast onset •short duration High absorption	•fast onset •short duration.	•Slow onset •intermediate duration of action	•Slow onset •long duration of action (almost 24 hours).
Ex	Lispro, aspart	regular insulin	lente, NPH	glargine

Notes:

1st ,2nd types used in :
1- emergency
2-postprandial hyperglycemia.
3rd, 4th types used in: type1 DM only as continuous source of insulin

1- Ultra-short acting insulins

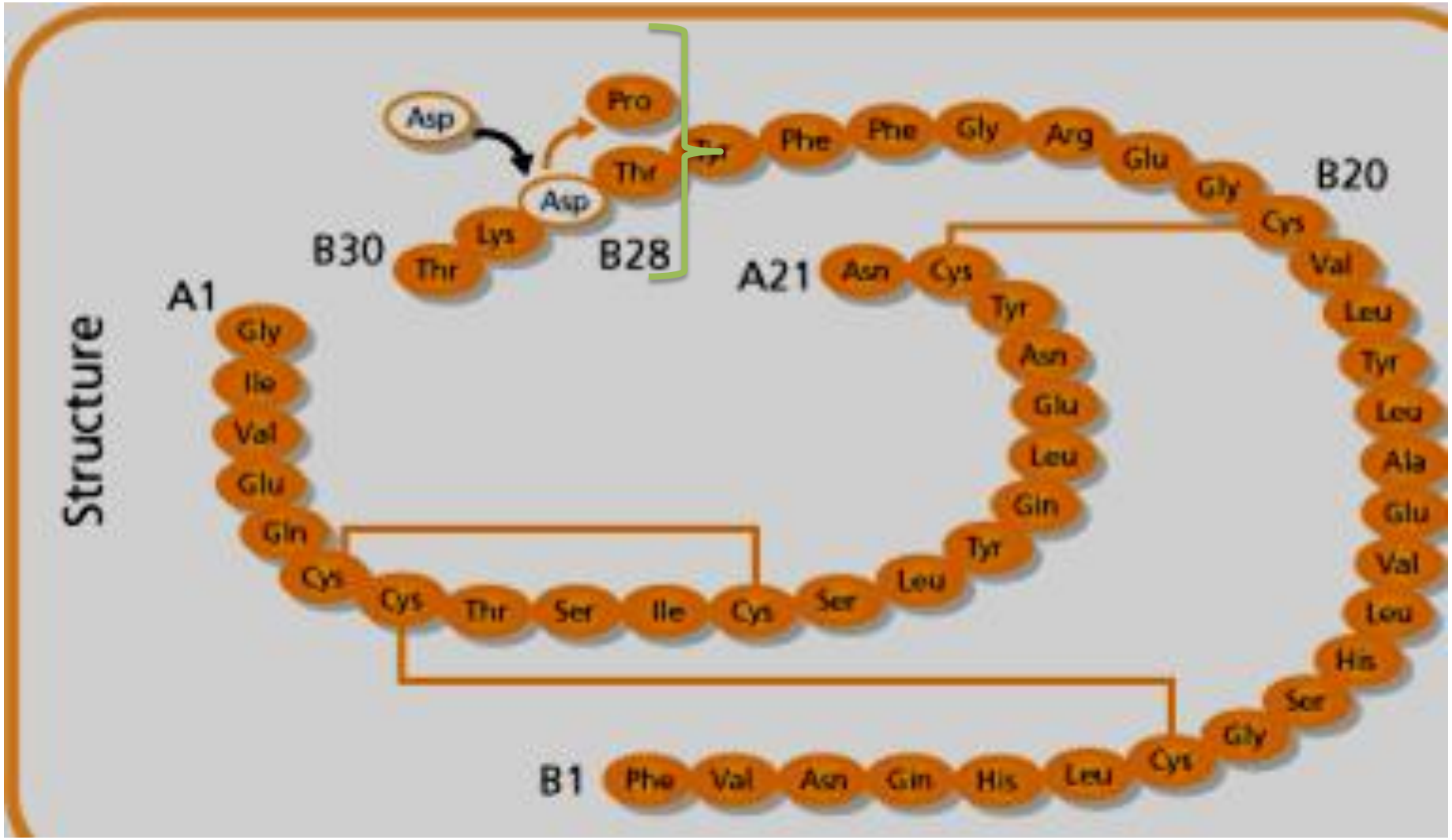
e.g: Insulin lispro, insulin aspart

(the names are given according to which amino acid is changed)

- **Clear solutions at neutral pH** >> it means no particles (clear sterile solution)>> no risk of thrombosis >> can be given I.V >> used in ER
- **Do not aggregate or form dimers or hexamers *(monomeric analogue to insulin).***

- ***Fast onset* of action (5-15 min)**
- ***Short duration* of action (3-5 h)**
- **Reach peak level 30-90 min after injection.**
- **S.C. (5 -15 min before meal).**
- **I.V. in emergency.**

Insulin aspart



- **2-3 times/day.**> Before each meal
- **Mimic the prandial mealtime insulin release**
- **Have the lowest variability of absorption**
- **Preferred for external insulin pump (*Lispro does not form hexamers*)**
- **used to control post-prandial hyperglycemia and emergency ketoacidosis.**
- This drug can`t be taken without long duration insulin >> to maintain the basal rate of insulin all the time not only after meals.. *It will be explained later* ..

2-Short acting insulins (regular insulin)

- **Soluble crystalline zinc insulin (stability – shelf half life)**
- **Clear solutions at neutral pH**>> can be given I.V
- **Forms hexamers.**> because of that it has onset of action slower than 1st type
- **Onset of action 30-45 min (S.C.)**.>> have to wait 30 min before eating .
- **Peak 2-4 h.**
- **Duration 6-8 h.**

Short acting insulins (regular insulin)

- **I.V. in emergency situations.**
  - **Management of ketoacidosis**
  - **After surgery**
  - **During acute infection Like sepsis**
- **2-3 times/day.**
- **Control postprandial hyperglycemia & ketoacidosis.**
- **Can be used in pregnancy**

*in case of pregnant lady stop oral hypoglycemia and give insulin especially regular insulin cause it's the most one similar to endogenous insulin.

	Short-acting (regular) insulins e.g. Humulin R, Novolin R	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	postprandial hyperglycemia & emergency diabetic ketoacidosis	postprandial hyperglycemia & emergency diabetic ketoacidosis
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
chemistry	Hexameric analogue	Monomeric analogue
Route & time of administration	-S.C. 30 – 45 min before meal -I.V. in emergency (e.g. diabetic ketoacidosis)	-S.C. 5 min (no more than 15 min) before meal -I.V. in emergency (e.g. diabetic ketoacidosis)
Onset of action	rapid 30 – 45 min (S.C)	Very Fast 5 – 15 min (S.C)
Peak level	2 – 4 hr	30 – 90 min
Duration	6 – 8 hr longer	3 – 5 hr Shorter
Usual administration	2 – 3 times/day	2 – 3 times / day

Advantages of Insulin Lispro vs Regular Insulin IMP !!

- **Rapid onset of action**

(due to rapid absorption)

- **Reduced risk of postprandial hypoglycemia**

(due to short duration of action)

3-Intermediate acting insulins

A) Isophane (NPH) insulin

(Humulin N, Novolin N)

B) **Lente insulin**

(Humulin L, Novolin L)

A) Isophane (NPH) Insulin

(Humulin N, Novolin N)

- **NPH, is a Neutral Protamine Hagedorn insulin in phosphate buffer.**

No need for memorizing the structure☺

- **NPH insulin is combination of protamine & crystalline zinc insulin (1: 6 molecules)> this complex has low rate of absorption ,delayed onset, long duration of action**
- **proteolysis release insulin.**

A) Isophane (NPH) Insulin

- **Turbid suspension at neutral pH.**
- **Given S.C. only not i.v.**
- **Can not be used in ketoacidosis or emergency**
- **Onset of action 1-2 h.**
- **Peak serum level 5-7 h.**
- **Duration of action 13-18 h.**

A) Isophane (NPH) Insulin

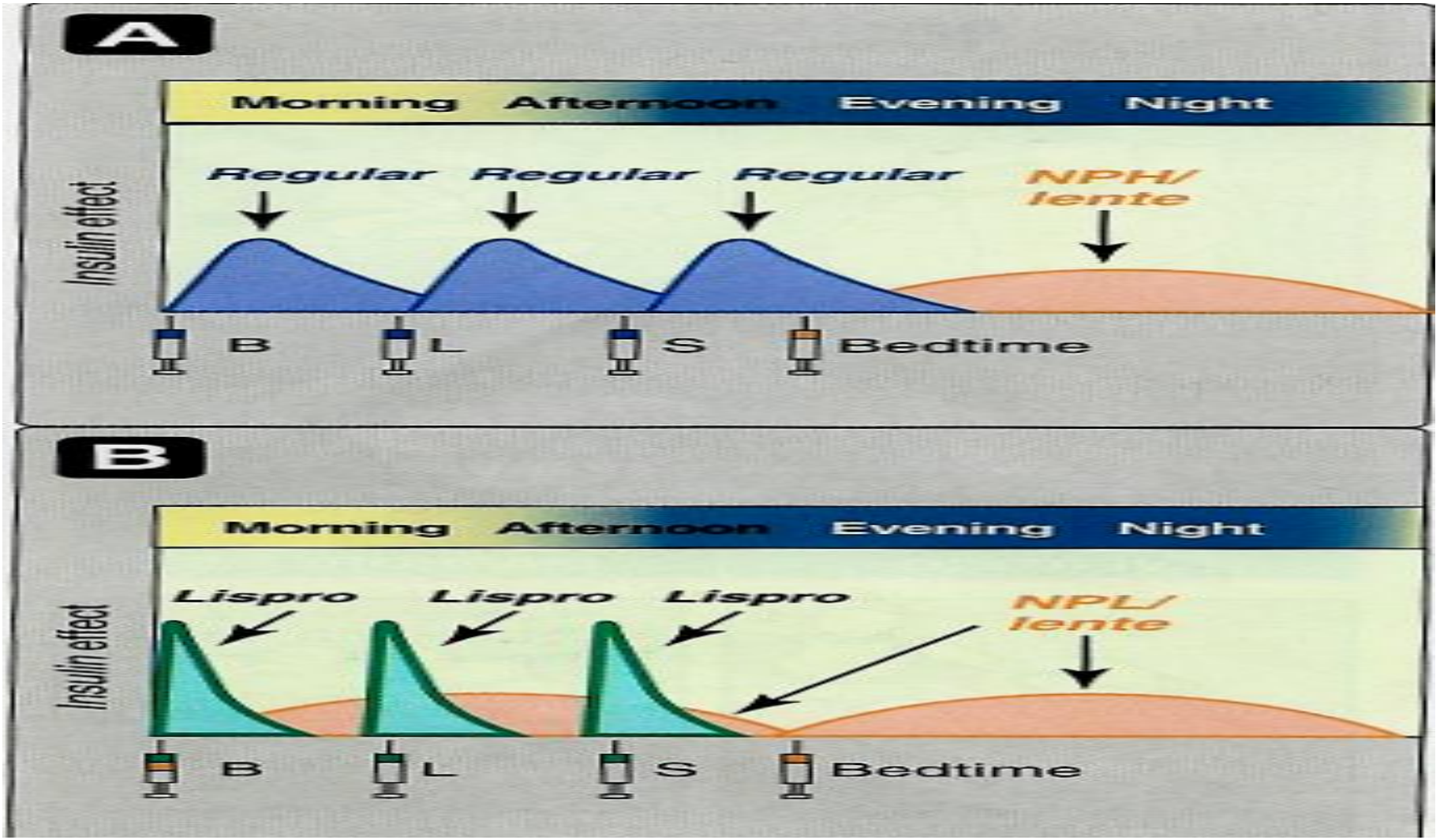
(the slide explains the effect of NPH when it is combined with ultra & short drugs)

Insulin mixtures

- **(NPL= NPH / lispro) (NPA= NPH / aspart)**
- **NPL & NPA have the same duration as NPH**
- **70/30 – 50/50 NPL/insulin lispro**
- **75/25 - 70/30 - 50/50 (NPH/regular).**

Prandial and basal insulin replacement

the pict. Explains how NPH/lente conserve the basal level of insulin at night



B) **Lente insulin**
(Humulin L, Novolin L)

- **Mixture of:**
  - **30% semilente insulin** ***(amorphous precipitate of insulin with zinc in acetate buffer)***
  - **70% ultralente insulin** ***(poorly soluble crystal of zinc insulin)***
- **Turbid suspension at neutral pH**
- **Given S.C., *not intravenously***

B) Lente insulin

- **Delayed onset of action (1-3 h)**
- **Peak serum level 4-8 h.**
- **Duration of action 13-20 h.**
- **Lente and NPH insulins are equivalent in activity.**
- **Lente is not used in diabetic ketoacidosis or emergency.**

Imp points of Intermediate acting insulins

- **Turbid suspension at neutral pH.**
- **Given S.C. only not i.v.**
- **Can not be used in ketoacidosis or emergency**
- **Lente and NPH insulins are equivalent in activity.**

4-Long acting insulins
Insulin glargine (lantus)

- **Slow onset of action 2 h.**
- **Clear solution BUT forms precipitate *(hexamer)* at injection site.(you may ask .. It is clear solution >> so can be given I.V ??? the answer is NO .. Why ?? Because it precipitates at the site of injection lead to have slow absorption)**

- **absorbed less rapidly than NPH & Lente insulin.**
- **Given s.c., *not intravenously***

Long acting insulins
Insulin glargine (lantus)

- **Maximum effect after 4-5 h**
- **Prolonged duration of action (24 h).**
- **produce broad plasma concentration plateau (low continuous insulin level)**

SO it controls the basal level very well by producing Constant circulating insulin
(المحافظة على معدل الانسولين الطبيعي طوال اليوم)

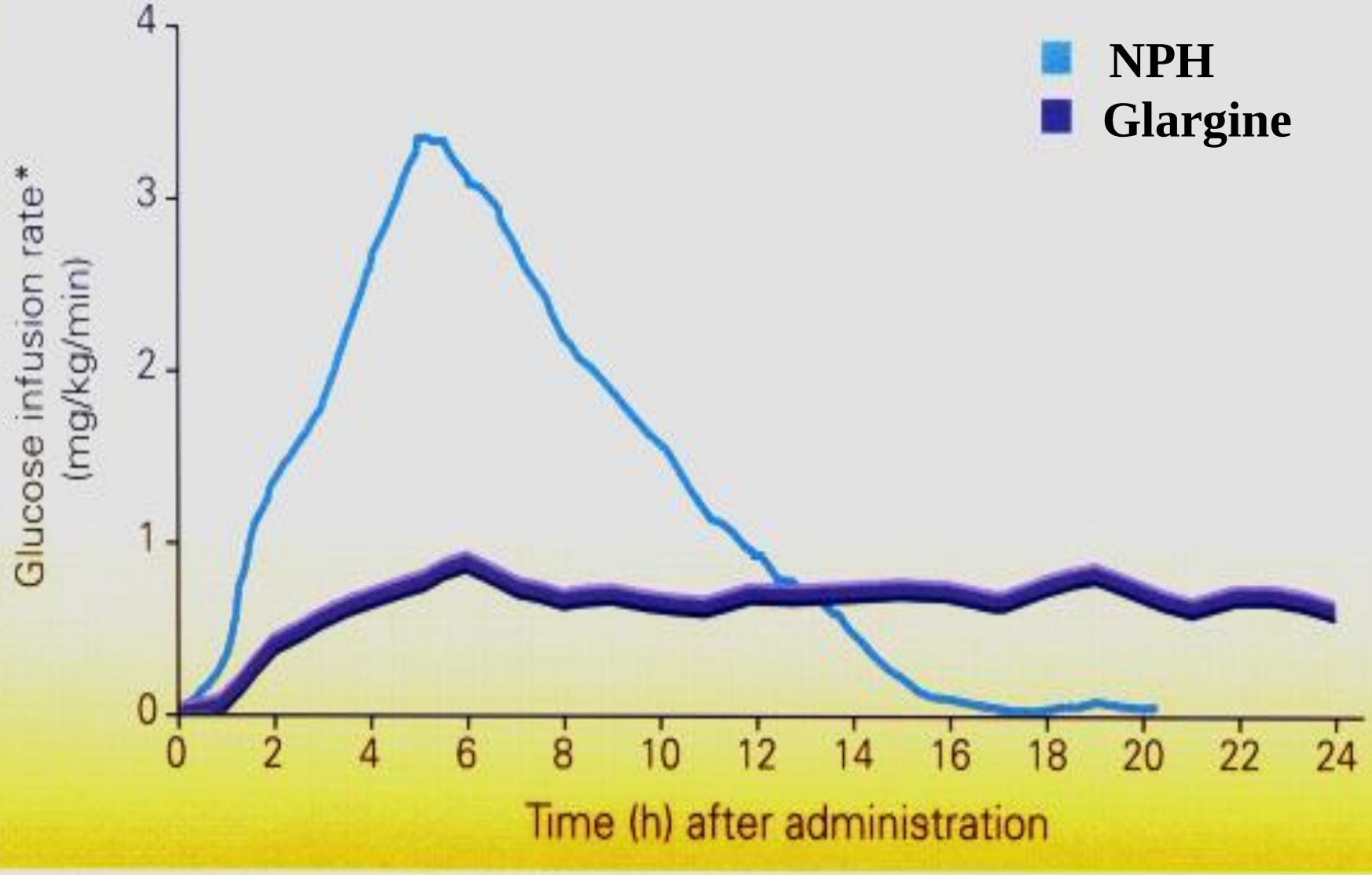
- **Once daily**

Advantages over intermediate-acting insulins: IMP!!

- **Constant circulating insulin over 24 hr with no peak (*peakless profile*).**
- **Produce flat prolonged hypoglycemic effect.**
- **More safe than NPH & Lente insulins**

(*reduced risk of nocturnal hypoglycemia*).

NPH *vs* Glargine



Complications of Insulin Therapy:

- **Hypoglycemia**

  When:

  - Overdose of insulin
  - Excessive (unusual) physical exercise
  - A meal is missed

- **Hypersensitivity reactions.**
- **Lipodystrophy at injection site**

(to avoid this the pt is advised to change the site of injection)

- **Weight gain *(due to anabolic effects of insulin)***
- **Insulin resistance**
- **Hypokalemia**

Summary

- **Insulin analogues are used to treat type I diabetes.**
- ***Fast acting insulins*** **(lispro, aspart, glulisine), given s.c. or i,.v., produce fast action, used to mimic postprandial insulin.**
- ***Short acting insulin (Regular insulin), given s.c. or i.v.*** **produce rapid action, used to mimic postprandial insulin.**
- ***Intermediate acting insulin (lente, Isophane)*** **produce slower action, than regular insulin, given s.c. not i.v.**
- ***Long acting insulins*** **(glargine) produce constant circulating insulin over 24 hr with no peak (peakless profile), s.c. not i.v.**

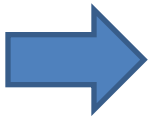
imp..Notes

- In **emergency** >> ultra short & short.
- Before meals we can use ultra short & short

But if someone wants to eat immediately not to wait 30 min ultra-short can be used

- Main complication **Hypoglycemia**
- In pregnancy use **regular insulin**
- **The treatment with** ultra short & short **should be combined with intermediate or long (long more preferred) .. Why ?**

Pt with DM type 1 there is No insulin at all So there is no thing conserve the basal level of insulin at night cuz the short & ultra-short only conserve at time of eating , because of that the pt is given long insulin at night ..



Short-acting (regular) insulins

e.g. Humulin R, Novolin R

Isophane (NPH)

(Humulin N, Novolin N)

Lente insulin

(Humulin L, Novolin L)

Ultra-Short acting insulins

e.g. Lispro, aspart, glulisine

Long acting insulins

Insulin glargine (lantus)