Endocrine System

PHARMACOLOGY 432 TEAM

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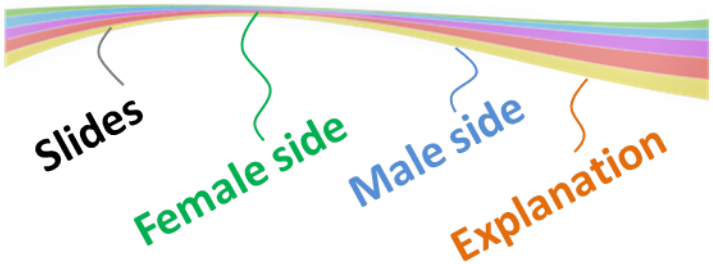
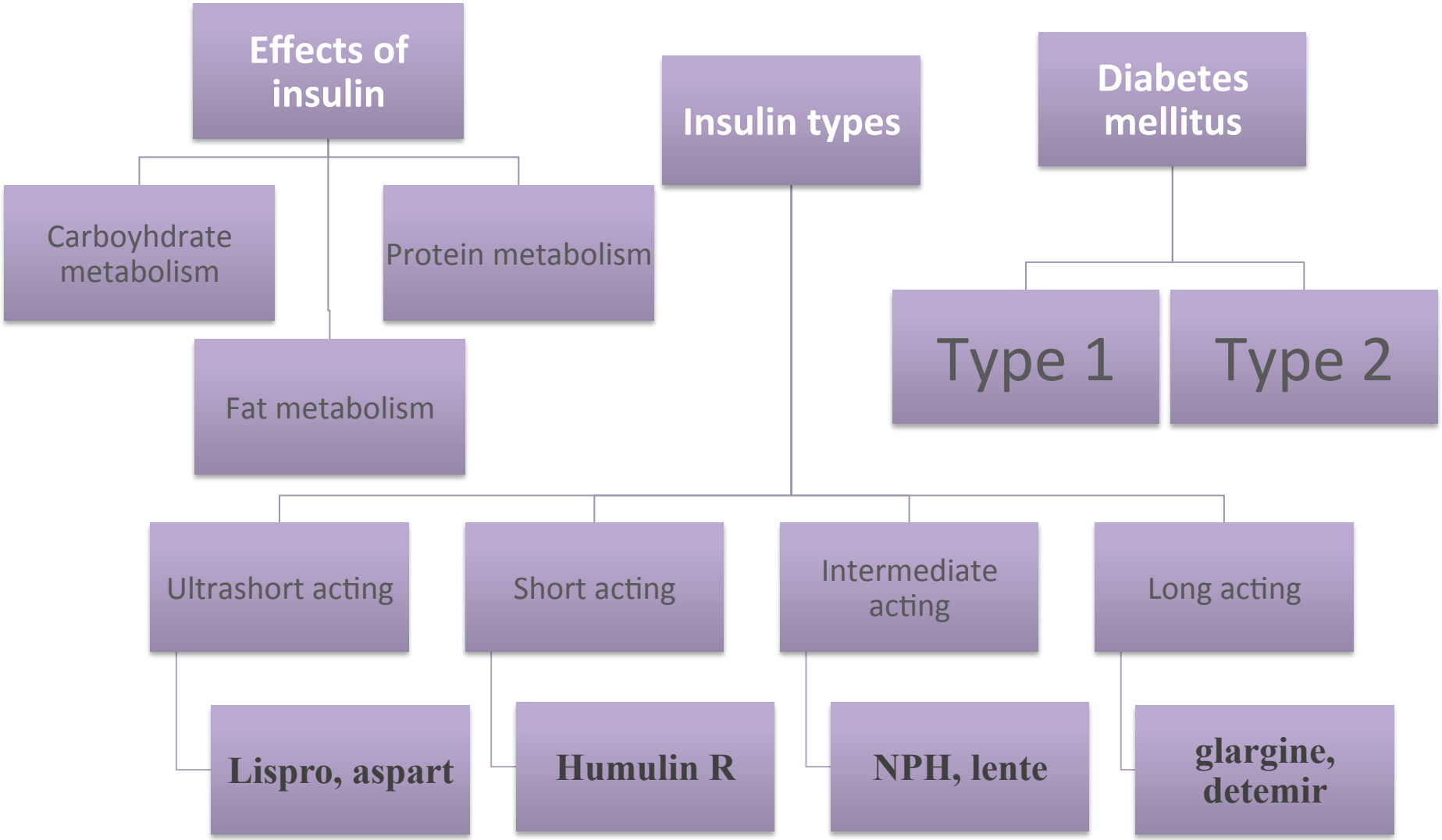


USE OF INSULIN IN THE TREATMENT OF DIABETES MELLITUS

Objectives:

- 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 of different insulin analogues.
- Know the uses of different insulin analogues

Mind Map


Effects of insulin
Carboyhdrate metabolism
Protein metabolism
Fat metabolism
Insulin types
Diabetes mellitus
Type 1
Type 2
Ultrashort acting
Short acting
Intermediate acting
Long acting
Lispro, aspart
Humulin R
NPH, lente
glargine, detemir

Endogenous Insulin

1. Basal level of insulin is 5-15 µU/ml. (produced even when there is no food)
2. Half life of circulating insulin is 3-5 min

N.B

Insulin levels peek during the three daily meal times due to their major stimuli ,glucose, however in between meals it returns back to its basal level.

Other release stimuli (GIT hormones , vagal stimuli , amino acid , and fatty acids)

Insulin receptors:

Present on cell membranes of most tissues as liver, muscles and adipose tissues

Effects of insulin

Carbohydrate Metabolism

- **Lowers of blood glucose by: (main goal)**
  - ↑ glucose uptake & utilization by peripheral tissue
  - ↑ Glycogen synthesis
  - ↑ Conversion of carbohydrate to fats.
  - ↓ Gluconeogenesis.
  - ↑ Glycolysis (muscle).

Fat Metabolism

- **Liver:**
  - ↑ Lipogenesis.
  - ↓ Lipolysis.
  - Inhibits conversion of fatty acids to keto acids.
- **Adipose Tissue:**
  - ↑ Triglycerides storage.
  - ↑ Fatty acids synthesis.
  - ↓ Lipolysis

Protein Metabolism

- **Liver:**
  - ↓ protein catabolism.
- **Muscle: (anabolic action)**
  - ↑ amino acids uptake.
- ↑ protein synthesis.
- ↑ glycogen synthesis (glycogenesis).

potassium

- ↑ potassium uptake into cells.

With Diabetes

↓ Glucose uptake	Hyperglycemia	Glycosuria	Dehydration
↑ Lipolysis	Plasma FFA	Ketosis	Acidosis
↑ AA mobilization	Plasma AA	Pyruvate	Glucose synthesis

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(126mg/dl) or
- Plasma glucose > 11.1 mmol/L (200mg/dl) 2h after a meal confirms a diagnosis of diabetes.

Type **I (IDDM)**
due to autoimmune or viral diseases

Type **II (NIDDM)**
due to obesity, genetic factors

Gestational
Occurs transiently in pregnancy

- The rest are micro-vascular

Complication of diabetes

- Neuropathy
- foot amputation
- retinopathy
- nephropathy
- Cardiovascular problems (macro-vascular)

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 % (more common)
Genetic predisposition	Moderate	Very strong
Defects	β-cells are destroyed	β-cells produce inadequate quantity of insulin
Endogenous insulin	Absent	Present (not enough) (partial deficiency)
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 (oral anti-diabetic) ±insulin

Insulin Preparation

	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine	Short-acting (regular) insulins e.g. Humulin R, Novolin R
Physical Characteristics	Clear solution at neutral pH so can be given IV. Can mimic the post prandinal insulin release	
Chemistry	Monomeric analogue	Hexameric analogue, soluble crystalline(more than 1 molecule) zinc insulin
Rout & time of adminstration	S.C. 5 min (no more than 15 min) before meal , you can eat after taking it	S.C. 30 – 45 min before meal
Onset of action	5 – 15 min (S.C) (very fast onset of action)	30 – 45 min (S.C) fast action
Peak level	30 – 90 min	2 – 4 hr
Duration	3 – 4 hr (very short duration)	6 – 8 hr short duration
Usual admistiration	2 – 3 times / day or more	2 – 3 times/day or more
Indication	✸ postprandial hyperglycemia (S.C) ✸ emergency diabetic ketoacidosis (I.V) ✸ Can be used in pregnancy (Regular insulin only)	

Insulin Preparation

Advantages of Insulin Lispro vs Regular Insulin:

- Rapid onset of action (patients will not wait long before they eat).(due to rapid absorption)
- Its duration of action is no longer than 3-4 hrs regardless of the dose.
- Decreased risk of postprandial hypoglycemia. due to sjort duration of action
- Decreased risk of hyperinsulinemia (due to sjort duration of action)

NORMALLY, Insulin is released in response to food, then glucagon come and antagonize it to make BALANCE.
But in with these drugs (exogenous insulin), patient develop postprandial hypoglycemia because there is nothing antagonize them.

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Insulin Preparation

	Intermediate acting insulins	
	Isophane (NPH) is a Neutral Protamine Hagoderon (complex of insulin) insulin in phosphate buffer	**Lente insulin**
Physical Characteristics	Turbid suspension at neutral pH (cant be given I.V). Both are equivalent in activity	
Rout	S.C. only NOT I.V	
Onset of action	1-2 h (slow onset of action)	1-3 h (slow onset of action)
Peak level	5-7 h	4-8 h
Duration	13-18 h (relatively long duration of actionc cuz it's a bigger molecule)	13-20 h (relatively long duration of action)
Composition	Combination of protamine and crystalline zinc insulin	30% semilente (means partial size half half) insulin + 70% ultralente (very big+long acting)insulin
Indication	✸ Not used in emergency or diabetic ketoacidosis	✸ Not used in emergency or diabetic ketoacidosis
Mixture	Can be mixed with ultrashort or short duration: NPL= NPH/ Lispro NPA = NPH/ Aspart 75/25 - 70/30 - 50/50 (NPH/regular) → With short acting insulin there is risk of hypergylcemia druing night bcuz of it's short duration, so we prescribe drugs with longer duration such as NPH (sometimes given 2/day) * We treat depending on blood glucose level	

Insulin Preparation

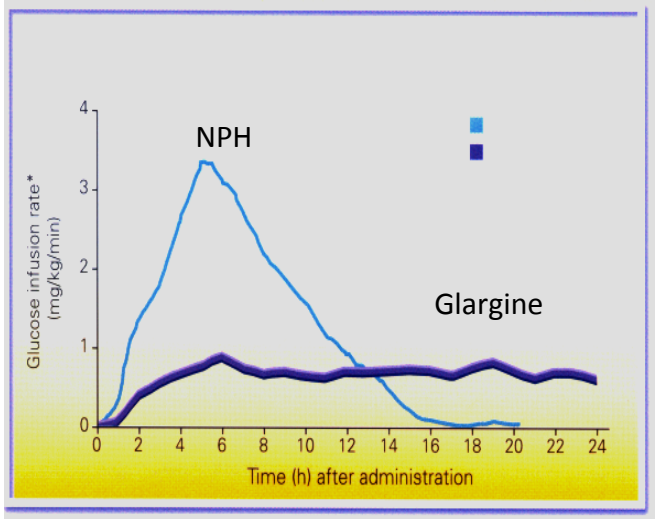
Long acting insulins,
detemir(Levemir)
Insulin glargine (lantus)

Should not be mixed with other insulin
All the above could be mixed except long acting)

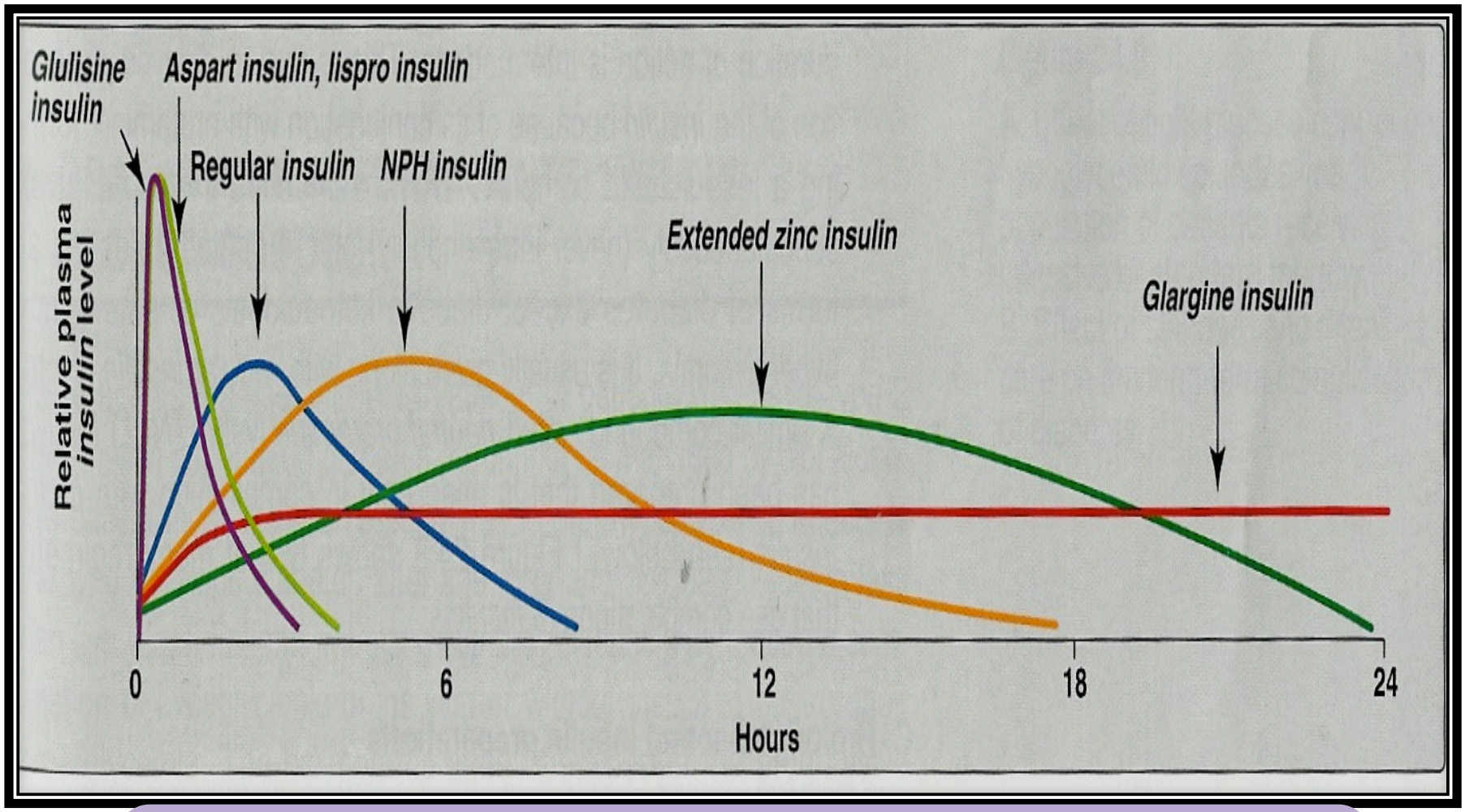
Physical Characteristics	Clear solution but precipitate at injection site
Rout	Given s.c not I.V.
Onset of action	2 h slow onset of action Absorption less rapidly than NPH & Lente insulin
Peak level	4-5 h **produce broad plasma concentration plateau** (low continuous insulin level).
Duration	Prolonged (24h)
Usual administiration	Once daily
	Produce broad plasma concentration plateau (low continuous (like panceras) level over 24 h low) (reduce risk of hyperinsulinemia)

Advantages of Insulin glargine over intermediate-acting insulins:

- Constant circulating insulin over 24 hr with **no pronounced peak**.(not absorbed rapidly)
- More safe than **NPH & Lente insulins** (reduced risk of hypoglycemia).
- NPH >> there is pronounced peak (maximum concentration)then decline in concentration



Insulin Preparation



Aspart produces peak with (short onse+duration)
NPH ponounce peak and shorter in action than Lente
Lente (extended zinc insulin)
Grigline (constant level with long duration)

Sources of Exogenous Insulin

- **Beef Insulin**
- **Porcine Insulin**
- **Human Insulin**

Both are not preferable due to Ag/Ab interaction , for the beef has three different amino acids in the insulin sequence than that of humans and the pork has one

Less immunogenic.

Prepared by recombinant DNA techniques (a method by which PCR amplification is used to read the 51 amino acid sequence in the human insulin → introduction to e-coli →they start to grow in number and so does the insulin ..etc. its along process but all you need to know is that it's a technique used when you want to match something with something found in the human body)

Modifications of amino acid sequence of human insulin can change its pharmacokinetics (absorption and duration of action) N.B

pharmacodynamics, the action, remains the same

Routes of administrations & degradation of insulin

- **Can not be given orally**(because they are amino acids and they will get destroyed)
- **Insulin is given subcutaneously (s.c) (most common method)**
- 1/ Insulin syringes **(s.c., arms, abdomen, thighs)**. (you need to change sight of entry otherwise lipodystrophy/Lipohypertrophy will happen)
- 2/ Portable pin injector **(pre-filled)**. — Good for kids
- 3/ Continuous S.C. infusion **(insulin pump)**.
  - More convenient
  - Eliminate multiple daily injection
  - Programmed to deliver basal rate of insulin
  - Disadvantage is 1-tendency to get infected 2-if adjusted to a certain dose yet person didn't eat he/she is at risk of developing hypoglycemia mainly seen in kids
  - **intravenously (in a hyperglycemic emergency)**

Pin injector

Insulin pump

- **60% liver & 40% kidney (endogenous insulin)**
- **60% kidney & 40% liver (exogenous insulin)**
- Should be stored in refrigerator& warm up to room temp before use.
- Must be used within 30 days.

Complications of Insulin Therapy

- **Hypoglycemia (life threatening occurs when blood glucose < 50 mg/dl)**

  Caused by:

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

  How it is treated?

  If Conscious patient: Sugar containing beverage or food (30 g orally).

  If Unconscious patient: 20-50 ml of 50% glucose solution I.V. infusion, OR Glucagon (1 mg S.C. or I.M.)

- **Weight gain(anabolic effect of insulin)**
- **Hypersensitivity reactions(rare)**
- **Lipohypertrophy = hypertrophy at injection site (don't inject at the same area many times)**
- **Insulin resistance(rare)**
- **Hypokalaemia**

Summery

- Diabetes type 1 patient with deficiency of insulin because of enormous beta-cell destruction. And **treatment includes**: dietary and exercise with **Insulin**.

- Diabetes type 2 patient have low-to-normal insulin levels and target-organ insulin resistance. And **treatment includes:** Dietary, Weight reduction, **Oral hypoglycemic agents as a monotherapy or combined with insulin.**

Types of insulin preparations :
Differs in pharmacokinetic properties mainly
Rate of absorption
Onset (time between time of injecting and action to occur) & duration of action
Variation is due to :
Change of amino acid sequence.
Size and composition of insulin crystals in preparations.
N.B whenever the rate of absorption is low , the release is slow and duration of action is longer and vise versa

- Ulterashort acting insulin: **Lispro & aspart.**
- Short acting insulin: **Regular insulin (Humulin R and novolin R).**
- Intermediate acting insulin: **Isophane (NPH) & Lente.**
- Long acting insulin: **detemir(Levemir) & Glargline (Lantus).**

- **Lispro** used for management of hyperglycemic emergencies.
- **Glargine** (Lantus) should not be mixed with other insulin.
- The standard route for administration of insulin is **subcutaneous injection**.

Questions

1. **Insulin can not be administered by:**

a) Oral route
b) Intravenous route
c) Subcutaneous route
d) Intramuscular route

2. **Main complications of insulin therapy include the following:**

a) Hypoglycemia
b) Insulin allergy
c) Lipodystrophy at an injection site
d) All of the above

3. **Which of the flowing statements is correct regarding insulin Glargine?**

a) It is primarly used to control postprandial hyperglycemia.
b) It is peakless insulin.
c) It is used in a regimen with insulin lispro or glulisine.
d) It may be administrated IV in emergency cases.

Answers: 1 - A , 2 - D , 3 - B

4. Pregnant type1 hyperglycemic patient, which treatment suits her ?:

a) Humilin R
b) Aspart
c) Lente
d) NPH

5. Patient came to ER with diabetic ketoacidosis , which drug can't be given to him ?

a)Aspart
b) Novolin R
c) Glulisine
d) NPH

Answers: 4 - A , 5 - D ,

Endocrine System

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