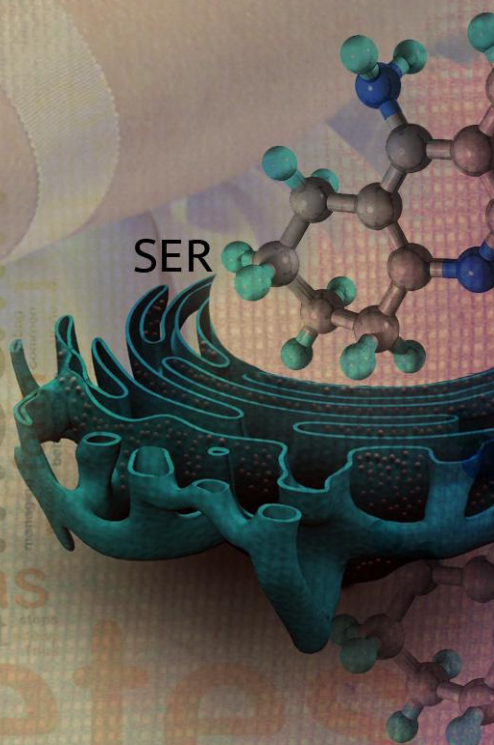
431 Teams
medical students

431 Team Pharmacology

Endocrine block

Lecture 6

Use of insulin in treatment of diabetes



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Introduction

❖ what is diabetes mellitus ?

A chronic metabolic disorder characterized by high blood glucose level caused by insulin deficiency and sometimes accompanied with insulin resistance.

❖ Glucose level ?

- Fasting plasma glucose > 7 mmol/L
- Plasma glucose > 11.1 mmol/L 2h after a meal

❖ complications ?

1- Cardiovascular problems
   - Micro-and macrovascular complications
   (i.e. atherosclerosis & arteriolosclerosis)
2- Renal failure (nephropathy).
3- Blindness (retinopathy).
4- Neuropathy.
5- Risk of foot amputation

What is normal blood glucose level ?

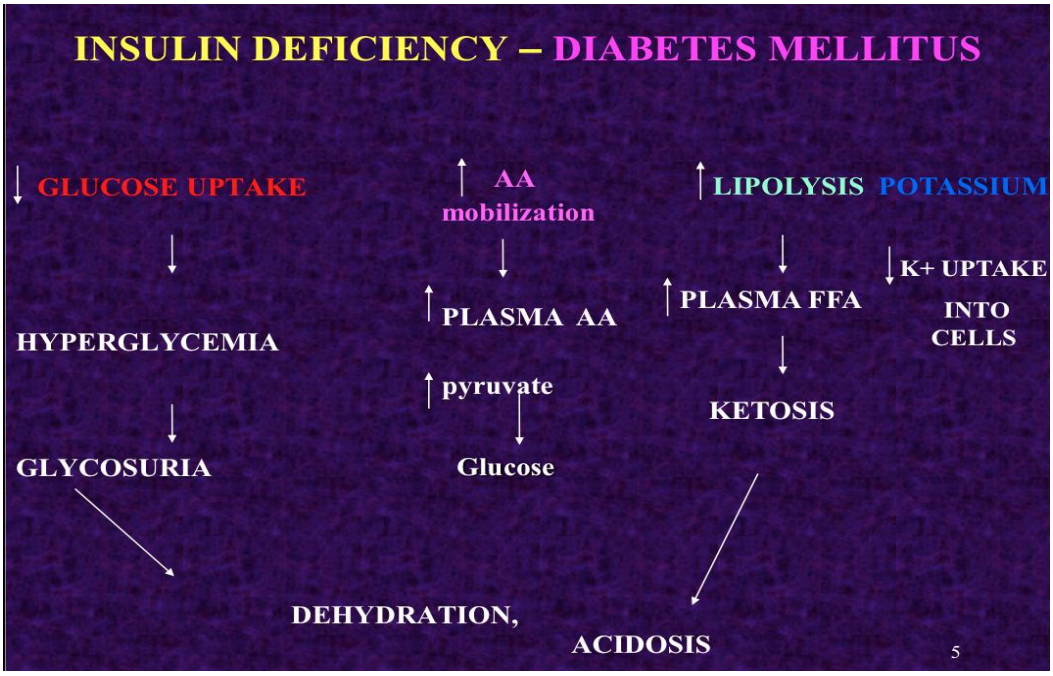
The American Diabetes Association recommends a post-meal glucose level of less than 10 mmol/L (180 mg/dL) and a fasting plasma glucose of 5 to 7.2 mmol/L (90–130 mg/dL)

Comparison between type 1 and type 2 diabetes mellitus

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 (obesity is a risk factor)
Ketosis	Frequent	Usually absent
Clinical symptoms	Polydipsia, polyphagia, polyuria, Wt loss	Often asymptomatic
lipid abnormalities	Hypercholesterolemia frequent	Cholesterol & triglycerides often elevated
Treatment	Insulin	Oral hypoglycemic ± Insulin

Effect of insulin

Lipid	Carbohydrate	Proteins
- Liver: ↑Lipogenesis. ↓ Lipolysis. fatty acids will not converted to keto acids. - Adipose Tissue: ↑ Triglycerides storage. ↑ Fatty acids synthesis. ↓ Lipolysis	Lowers of blood glucose by: ↑glucose uptake & utilization ↑ Glycogen synthesis ↑ Conversion of carbohydrate to fats. ↓ Gluconeogenesis. ↑ Glycolysis (muscle). ---------- ↑potassium uptake into cells.	Liver: ↓protein catabolism. Muscle: ↑amino acids uptake. ↑protein synthesis. Glycogen synthesis (glycogenesis).



Pharmacology of Insulins used in diabetes

❖ Types of insulin preparations :

They vary in onset and duration of action

1. **Ultrashort acting insulins e.g. Lispro, aspart (very fast onset and short duration)**
2. **Short acting insulins e.g. Regular insulin ,Humulin R (fast onset and short duration)**
3. **Intermediate acting insulin e.g. NPH, Isophane (lente) (slow onset, intermediate duration of action)**
4. **Long acting e.g. insulin glargine, detemir (Slow onset and long duration of action)**

Important points !

❖ There are only injected forms of insulins(IV/SC) , because insulin is broken down if taken orally !

❖ 1&2 are universal types , meaning they can be used both in type 1/ type 2 diabetes

❖ 1&2 are the ONLY types that could be used IV (due to their fast onset of action)

❖ 3&4 should not be used in type 2 diabetes (only for type 1)

1- Ultra-short acting insulins e.g. Insulin lispro ,Insulinaspart :

- **Clear solutions at neutral pH.**(clear= can be given IV)
- **Monomeric analogue.**(Monomeric means it is ready to bind to receptors " biologically active ")
- **mimic the prandial mealtime insulin release**
- **Fast onset of action (5-15 min)**
- **S.C. (5 min no more than 15 min before meal).**
- **Short duration of action (3-5 h)**
- **2-3 times/day**
- **Uses: Control postprandial hyperglycemia(s.c.) & emergency diabetic ketoacidosis(i.v)**

2- Short acting insulins (regular insulin) :

- **Clear solutions at neutral pH.**
- **Hexameric analogue.** (needs to be converted to monomeric to be bind on receptors)
- **Fast Onset of action 30-45 min (s.c.).**
- **Can mimic postprandial insulin release**
- **Short duration of action (6-8 h)**
- **Peak 2-4 h.**
- **2-3 times/day**
- **Uses: Control postprandial hyperglycemia(s.c), emergency ketoacidosis (i.v) & Pregnancy**
- (Pregnant diabetic woman and she is taking oral hypoglycemic drug she has to switch to insulin)and the best one for pregnant woman is regular insulin.

❖ **Advantages of Insulin Lispro vsRegular Insulin:**

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

3- Intermediate acting insulins (e.g.Isophane (NPH), Lenteinsulin) :

3.A- Isophane NPH

- **Turbid suspension at neutral pH**
- **Given S.C. only !! (only 1&2 are available as IV as we said earlier)**
- **Onset of action 1-2 h.**
- **Duration of action 13-18 h.**
- **Not used in emergencies (diabetic ketoacidosis).**

❖ **Insulin mixtures :**

- **75/25 - 70/30 - 50/50 (NPH/regular).**
- **(NPL= NPH / lispro)(NPA= NPH / aspart)**
  - ➢ mixtures have the advantages of having both intermediate and short actions + less number of injections

3.B- Lente insulin

- **Turbid suspension at neutral pH.**
- **Mixture of 30% semilente insulin + 70% ultralente insulin**
- **Given S.C.**
- **onset of action (1-3 h)**
- **Duration of action 13-20 h.**
- **Lente and NPH insulins are equivalent in activity.**
- **Not used in emergencies (diabetic ketoacidosis).**
  - ➢ Lente cannot be mixed with other fast acting insulins

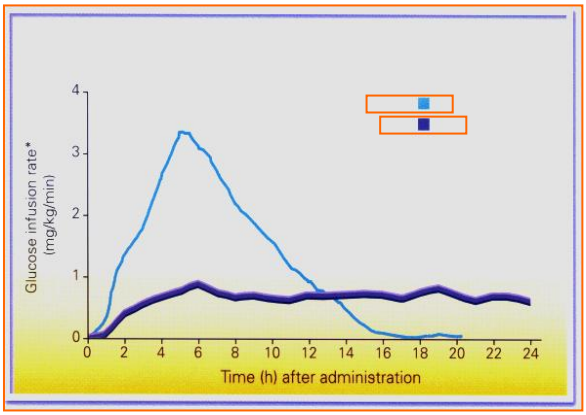
4- Long acting insulins **glargine** (lantus), **detemir**(Levemir) :

❖ Insulin Glargine :

- **Clear solution BUT forms precipitate at injection site** (change in the ph)
- **Slow onset of action 2 h.**
- **Given s.c.**
- **produce broad plasma concentration plateau (low continuous insulin level).**
- **Prolonged duration of action (24 h).**
- **Once daily**
- **Should not be mixed with other insulin**

❖ Advantages of Insulin glargine over intermediate-acting insulins :

- **Constant circulating insulin over 24 hr with no pronounced peak.**
- **More safe than NPH &Lenteinsulins(reduced risk of hypoglycemia) *(nocturnal hypoglycemia)***
- **We can see in the diagram the constant plateau of glargine> no peak > reduced risk of hypoglycemia**



❖ What are the route of administration of insulins ?

- **Insulin syringes (s.c., arms, abdomen, thighs).**
- **Portable pin injector (pre-filled).**
- **Continuous S.C. infusion (insulin pump).**
  - **I. More convenient**
  - **II. Eliminate multiple daily injection**
  - **III. Programmed to deliver basal rate of insulin.**

➢ Remember : earlier mentioned that insulins cannot be given orally, because insulin is polypeptide, if given orally it will be broken down by GI enzymes and acidity > no benefit

❖ Insulin degradation

- **Basal level of insulin is 5-15 µU/ml.**
- **Half life of circulating insulin is 3-5 min.**

❖ Complications of Insulin Therapy:

- **Hypoglycemia(we reduce the dose in case of these conditions)**
  - **a. Overdose of insulin**
  - **b. Excessive (unusual) physical exercise**
  - **c. A meal is missed**
- **Weight gain(lipogenic effect of insulins)**
- **Hypersensitivity reactions(rare)**
- **Lipodystrophy at injection site(avoided by changing site of injections)**
- **Insulin resistance(rare)**
- **Hypokalaemia(insulin moves potassium into the cell > less in blood)**

Summary

	Short-acting insulins e.g. regular insulin	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	postprandial hyperglycemia & emergency diabetic ketoacidosis	postprandial hyperglycemia & emergency diabetic ketoacidosis
chemistry	Hexameric analogue	monomeric
Physical	Clear solution at neutral pH	Clear solution at neutral pH
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	30 – 45 min (S.C)	0 – 15 min (S.C)
Peak level	2 – 4 hr	30 – 90 min
Duration	6 – 8 hr	3 – 5 hr
Usual administration	2 - 3 times/ day or more	2 – 3 times/ day or more

- **Ultra-short and short acting we don't use them alone we should give long or intermediate acting insulin before sleep.**
- **Best drug for pregnancy is regular insulin**
- **NPH, lente, and glargine are available in S.C. form only(not used in emergency)**
- **NPH can be mixed with regular insulin or lispro**

- **NPH and lente are equivalent in activity**
- **Glargine> no peak with prolonged duration > less risk of hypoglycemia > once daily ,so it is more save than intermediate acting insulin at the night**
- **Hypoglycemia is most common complication of insulin therapy**

Questions

1- insulin cannot be administrated ?
A. Oral route
B. Intravenous route
C. Subcutaneous injection
D. Subcutaneous infusion

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 following should be administered to achieve rapid control in a patient suffering from severe ketoacidosis ?
A. Lispro
B. Glyburide
C. Glargine
D. NPH

4- Which of the following statements is correct regarding insulin glargine?
A. It is primarily used to control postprandial hyperglycemia.
B. It is a“peakless” insulin.
C. The prolonged duration of activity is due to slow dissociation from albumin.
D. It should not be used in a regimen with insulin lispro or glulisine.

A-D-A-B

Good Luck