Revised & Approved

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Pharmacology 439

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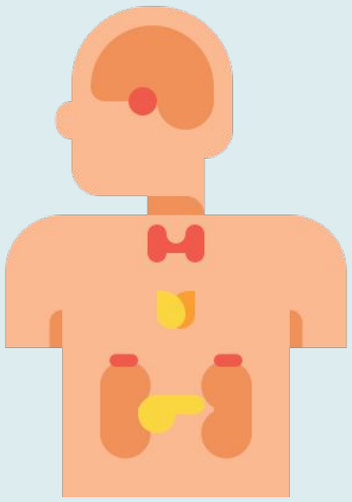

Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Use of insulin in treatment of diabetes (T1DM)

Objectives:

1- Define diabetes and mention different types of diabetes.

2- Differentiate between difference in treating type 1 and type 2 diabetes.

3- Understand mechanism of action, secretion, and actions of insulin.

4- Describe different types of insulin analogues

5- Be able to recognize the difference in pharmacokinetic profile between

6- Know uses of different insulin analogues.

Editing file | Summary

Diabetes mellitus

Is a chronic metabolic disorder characterized by high blood glucose level caused by deficiency of insulin or by increased insulin resistance.

Fasting plasma glucose (no food for 8 hrs)

Normal

<**100** mg/dl (5.6 x18 mmol/l).

Pre-diabetes

100-125 mg/dl (5.6-6.9 mmol/L).

Diabetes

Fasting >**126** mg/dl (7 mmol/L)

or

2h after a meal > **200** mg/dl (11.1 mmol/L).

Characteristic	Type 1 diabetes (insulin dependent diabetes mellitus (IDDM)) due to autoimmune or viral diseases	Type 2 diabetes (non insulin dependent diabetes mellitus (NIDDM)) due to genetic susceptibility and other risk factors (age, obesity).
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 **completely destroyed**	β-cells produce **inadequate** quantity of insulin
Endogenous insulin	Absent	Present (not enough)
Insulin resistance	Absent	Present (**in peripheral tissues**)
Nutritional status	Usually thin	Usually obes **(Obesity is an important factor)**
Ketosis	Frequent	Usually absent
Clinical symptoms	Polydipsia, polyphagia, polyuria, weight loss	Often asymptomatic
Related lipid abnormalities	Hypercholesterolemia frequent	Cholesterol & triglycerides often elevated
Treatment	**Insulin injection**	**Oral hypoglycemic drugs** (antidiabetic drugs)
Complications of diabetes	1. **B**lindness (retinopathy). 2. **N**europathy 3. **C**ardiovascular problems :Micro- and macro-vascular disease 4. Risk of foot **A**mputation 5. **R**enal failure (nephropathy)	

Bean's Car
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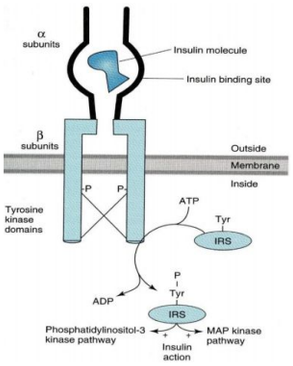
Insulin

Receptors

- Present on cell membranes of most tissues.
- Liver, muscle and adipose tissue.
- Pancreas beta cells → Proinsulin → Insulin + C - Peptide



Mechanism of action

1. Insulin binds to tyrosine kinase
2. Phosphorylation of **IRS-1** and **IRS-2** (insulin receptor substrate)
3. → binding and activating other kinases (e.g., PI3-K signaling pathway) or bind to adaptor proteins (e.g. growth factor receptor-binding protein 2) that translates insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein RAS (The gene family RAS encodes small GTPases that are involved in cellular signal transduction), and the MAPK (mitogen-activated protein kinase) system.

Interaction with Receptor

Results in multiple effects including:

- **Translocation** of glucose transporters (**GLUT**) to cell membrane with resulting **increase in blood glucose uptake**
- Glycogen synthase activity and **increased glycogen formation**
- **Effects on protein synthesis**
- **Lipogenesis**
- **Activation of transcription factors**

Effects of insulin

Carbohydrate Metabolism

REMEMBER insulin function is anabolic

- ↑ Glucose uptake & utilization by peripheral tissues (Translocation of glucose transporters (GLUT-4) to cell membrane)
- ↑ Glycogen synthesis (glycogen synthase)
- ↑ Conversion of carbohydrate to fats.
- ↓ Gluconeogenesis.
- ↓ Glycogenolysis (liver)
- ↑ 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

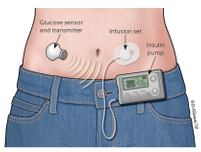
- **Liver:**
- ↓ protein catabolism.
- **Muscle:**
- ↑ amino acids uptake.
- ↑ protein synthesis
- ↑ glycogen synthesis (glycogenesis).

potassium

- ↑ potassium uptake into cells.

Insulin, cont.

Pharmacokinetics

Routes of administrations of exogenous insulin	**Can not be given orally why?** because its a protein and it will be digested (destruction by PH) ▪ Insulin syringes (**S.C.**, arms, abdomen, thighs). ▪ Portable pen injector (pre-filled). ▪ Continuous S.C. infusion (insulin pump): 1- More convenient 2- Eliminate multiple daily injection 3 -Programmed to deliver basal rate of insulin. ▪ **Intravenously IV** (in a hyperglycemic emergency) ▪ Inhaled aerosols, transdermal, intranasal (**Under Clinical Trials**).  
Insulin degradation	● Basal level of endogenous insulin is **5-15 µU/ml** ● Half life of circulating insulin is 3-5 min. ● 60% liver & 40% kidney (**endogenous** insulin) ● 60% kidney & 40% liver (**exogenous** insulin) Be careful when prescribe insulin to patient with renal disorder which may cause toxicity and severe hypoglycemia

Source

Exogenous	**Beef Insulin**: Differs from human insulin by 3 amino acids (antigenic). **Porcine Insulin**: Differs by one amino acid (antigenic).
Human Insulin analogues	Prepared by recombinant **DNA techniques**. ● **Less immunogenic**. ● Modifications of amino acid sequence of human insulin can change pharmacokinetics .

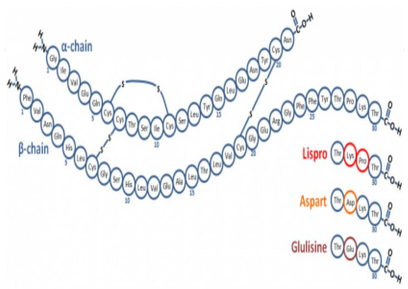
Types of insulin preparations

- Differ in **pharmacokinetic properties** mainly
  - Onset of action (Rate of absorption).
  - Duration of action.
- **Variation is due to:**
  - Change of amino acid sequence. changes pharmacokinetics of insulin ONLY. pharmacological action is not affected.
  - Size and composition of insulin crystals in preparations (monomers, dimers, hexamers).
    Monomers are small and this why it have fast onset of action but less duration of action.

1- Ultra-short acting insulins	2- Short acting insulins	3- Intermediate acting insulins	4- Long acting insulins
e.g. Lispro, Aspart, glulisine. Very fast onset of action and short duration.	**e.g. Regular insulin, Humulin R**egular**, Novolin R** Fast onset of action and short duration.	**e.g. NPH, Lente.** Slow onset, intermediate duration of action.	**e.g. Glargine, Detemir.** Slow onset and long duration of action (24hrs).

Insulin

1- Ultra-short acting insulins

Drug	Insulin **Lispro** (Humalog®), insulin **Aspart** (Novolog®)
P.k	• **Clear solutions** at neutral pH. It has to be clear so it can be used as IV • Do not aggregate or form dimers or hexamers **(monomeric** (Monomer = 1 unit) **analogue)** this is why it's short acting. • Fast onset of action **(5-15 min)** • Short duration of action **(3-5 h)** • S.C. (5 -15 min before meal). • Reach peak level 30-90 min after injection. • 3 times/day (before each meal). • Mimic the prandial mealtime insulin release. • **I.V in emergency.** in case of diabetic ketoacidosis (DKA) 
Uses	• Preferred for external insulin pump • Used to control postprandial hyperglycemia (S.C.) and **emergency** (best) **diabetic ketoacidosis (I.V)** (clear solution)

2- short acting insulins

Drug	**Humulin (Regular insulin)**
P.K	• Soluble crystalline zinc insulin just like endogenous insulin that is also found linked to zinc • **Clear** solutions at neutral pH • Forms hexamers (aggregate not monomers) take more time to give its action in compare to Ultra short acting drug • Onset of action **30-45 min** (s.c.) • Duration **6-8 h** (longer) • **I.V. in emergency situations** • Peak 2-4 h • 2-3 times/day
Uses	• Control postprandial hyperglycemia (S.C.) & **emergency diabetic ketoacidosis (I.V)** ★ **Can be used in pregnancy** (DOC, even in T2DM)

Comparison between Ultrashort and short acting insulins

Characteristic	**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	
chemistry	**Monomeric** analogue	**Hexameric** analogue
Route & time of administration	• S.C. 5 min (≤15 min) before meal • I.V. in emergency (e.g. DKA)	• S.C. 30–45 min before meal • I.V. in emergency (e.g. DKA)
Onset of action	**Fast** 5–15 min (S.C)	**rapid** 30–45 min (S.C)
Peak Level	30–90 min	2–4 hr
Duration	3–5 hr **(Shorter)**	6–8 hr **(Longer)**
Usual administration	2–3 times/day	2–3 times/day
Uses	postprandial hyperglycemia & **emergency diabetic ketoacidosis (DKA)**	

Advantages of Ultra-short vs Short Insulin

- Rapid onset of action (patients 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 hyperinsulinemia.**
  - Decreased risk of postprandial hypoglycemia.

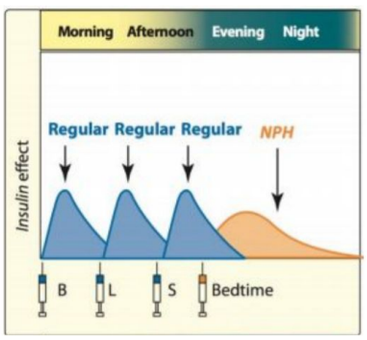
3- Intermediate acting insulins

Drug	1- Isophane (NPH) insulin
Characteristics	• **NPH**, is a **N**eutral **P**rotamine **H**agedorn insulin in phosphate buffer. • NPH insulin is combination of protamine & crystalline zinc insulin (**1:6** molecules) (large MW) proteolysis release insulin.
P.k	• Turbid suspension at neutral pH • Given S.C. only, **not I.V** because it's not a clear solution • **Can't** be used in ketoacidosis or emergency due to the slow onset • Onset of action **1-2 h** • Duration of action **13-18 h** • Peak serum level 5-7 h
Insulin Mixtures	1. NPH/regular insulin: 75/25, 70/30, 50/50 . 2. (NP**L** = NPH/**L**ispro) (NP**A** = NPH/**A**spart), NPL & NPA have the same duration as NPH, have two peaks. First peak due to ultra short acting part of the preparation, second peak due to NPH

3- Intermediate acting insulins, cont.

Drug	2- Lente insulin (Humulin L*, Novolin L) **Humulin and Novolin** are identical but with different name due to the difference in manufacturing companies *As we said before, when you see R after the drug = Regular and when you see L = Lente
Characteristics	• Mixture of: - 30% semilente insulin **(amorphous** (more soluble) **precipitate of zinc insulin in acetate buffer)** - 70% ultralente insulin **(poorly soluble crystal of zinc insulin)** • **Turbid suspension** at neutral pH. • Given S.C., **Not intravenously (I.V)** **Not use in emergency**
P.k	• 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.

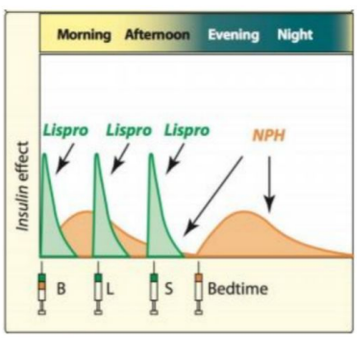
Prandial and basal insulin replacement (special thanks to 436 team)



Intermediate & Short acting insulin:

Before meals: diabetic patients takes short acting insulin which is regular insulin used to cover the daily need of the insulin after meals.

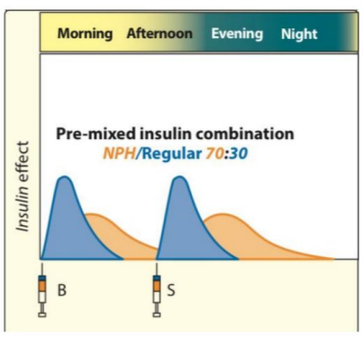
Before sleeping: no need for strong and fast action because glucose levels before sleeping aren't high like after meals so, to avoid hypoglycemia and coma the patients takes intermediate insulin.



Intermediate & Ultra-short acting insulin:

Same idea but the short acting insulin is replaced with the ultra-short acting insulin which has a rapid effect as long as the body needs the insulin as a basal level between meals.

The patients take double dose of the insulin intermediate to control the glucose level **for the whole day** not only before meals or sleeping time.



Insulin mixture (combination) = intermediate + short acting insulin:

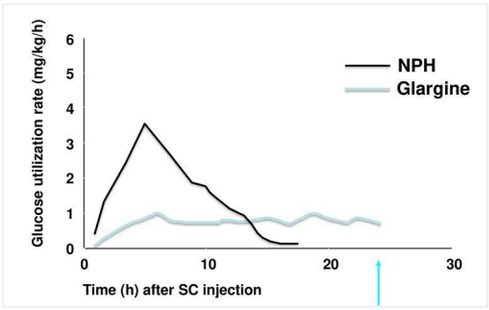
A helpful drug to reduce the use of injections for the diabetic patients and provide a basal level of insulin during the day.

Once the patient eats a meal short acting insulin is ready to act

4- Long acting insulins

Insulin Glargine (Lantus®), Insulin Detemir (Levemir®)

Drug	Insulin glargine (Lantus®)
Characteristics	• Clear solution **BUT forms precipitate (hexamer)** at injection site due to PH. • Slow onset of action 2 hr • Absorbed less rapidly than NPH & Lente insulin • Given S.C. only, **Not intravenously so not for emergency** • **Should not be mixed** with other insulins in the same syringe.
P.k	• Maximum effect after 4-5 h • **Prolonged duration of action (24 h)** • Once daily. Which is more convenient for the patient • Produce broad plasma concentration plateau **(low continuous insulin level)** (see figure 1) • Glargine must be used in regimens with rapid or short acting insulins to produce peaks at meal times
Advantages over intermediate-acting insulins	• Constant circulating insulin over **24 hr**, with no peak **(peak-less profile).** • **Produce flat prolonged hypoglycemic effect.** (the effect is not as strong as the others) • Reduced risk of nocturnal **hypo**glycemia → Safer than NPH & Lente insulins.



(figure 1)

Comparison between the onset and the duration of actions

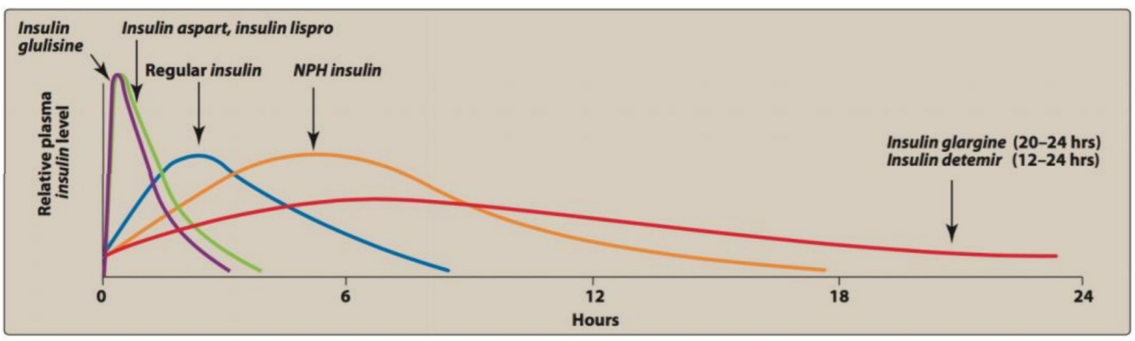


Figure 24.7
Onset and duration of action of human *insulin* and insulin analogs. NPH = neutral protamine Hagedorn.

Insulin

Insulin Dosing considerations

- **Blood glucose monitoring** is required in all patients receiving insulin
- Rotate injection sites within the same region
- Insulin should be stored in refrigerator and warm up to room temp before use

Complications of insulin

1. **Hypoglycemia**
2. Hypersensitivity Reactions (rare); human derivatives
3. Lipodystrophy (a buildup of fatty tissue) at the injection sites. (switch between injection sites)
4. Weight gain (Due to anabolic effects of insulin)
5. Insulin resistance we can combine other drugs of T2DM to manage it; T2DM drugs can be used in T1DM in certain cases
6. Hypokalemia (increased uptake of K^+)

Summary (Slides)

Insulin analogues are used to treat type 1 diabetes.

Fast acting insulins (lispro, aspart)	• Given S.C. or I.V. • produce fast action, used to mimic postprandial insulin.
Short acting insulin (Regular insulin)	
Intermediate acting insulin (lente, Isophane)	• Given S.C. **NOT** I.V. • slower action, than regular insulin
Long acting insulins (glargine, detemir)	• Given S.C. **NOT** I.V. • Produce constant circulating insulin over 24 hr with no peak (peakless profile)

Summary

*It's **IMPORTANT** to know the drugs included in each class and the ® name!

Insulin MOA	1. Phosphorylation of **IRS-1** and **IRS-2** (insulin receptor substrate) 2. → binding and activating other kinases : or bind to adaptor proteins that translates insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein RAS and the MAPK system .

Class*	Drug	Pk	Uses
1- Ultra short acting insulin	**Insulin lispro, insulin aspart**	**- Clear solutions** at neutral pH. - Do not aggregate (monomeric analogue) - Fast onset of action **(5-15 min)** Short duration of action **(3-5 h)** - S.C. (5 -15 min before meal). - Reach peak level 30-90 min after injection. - 3 times/day - Mimic the prandial mealtime insulin release.	- external insulin pump - Used to control postprandial hyperglycemia **(s.c.)** - **emergency** diabetic ketoacidosis **(I.V)**
2- short acting insulins	**Humulin (Regular insulin)**	- Soluble crystalline zinc insulin **- Clear** solutions at neutral pH - Forms hexamers - Onset of action **30-45 min** (s.c.) - Duration **6-8 h** - Peak 2-4 h - 2-3 times/day	- Control postprandial hyperglycemia (s.c.) & emergency diabetic ketoacidosis (I.V) **- Can be used in pregnancy**
3-Intermediate acting insulins	**1- Isophane (NPH) insulin** - Neutral Protamine Hagedorn insulin in phosphate buffer. - is combination of protamine & crystalline zinc insulin proteolysis release insulin. **Insulin mixtures:** 1- NPH/regular insulin 2- (NPL= NPH / Lispro) (NPA= NPH / Aspart) NPL & NPA have the same duration as NPH,	Turbid suspension at neutral pH Given S.C. only, **Not I.V** Onset of action **1-2 h** Duration of action **13-18 h** Peak serum level 5-7 h	**Can't be used in ketoacidosis or emergency**
	2- Lente insulin (Humulin L, Novolin L) Mixture of : - 30% semilente insulin (amorphous precipitate of zinc insulin in acetate buffer) - 70% ultralente insulin (poorly soluble crystal of zinc insulin) Turbid suspension at neutral pH. **Given S.C.**	- 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.	
4- Long acting insulins	**Insulin glargine (lantus®)** - Clear solution BUT forms precipitate (hexamer) at injection site - Slow onset of action 2 hr - Absorbed less rapidly than NPH & Lente insulin **- Given S.C. only, Not intravenously** **-Should not be mixed with other insulins in the same syringe.**	- Maximum effect after 4-5 h - Prolonged duration of action (24 h) - Once daily. - Produce broad plasma concentration plateau (low continuous insulin level) - Glargine must be used in regimens with rapid or short acting insulins	

MCQs

Q1: Which of the following insulins can be administered intravenously?			
A- Insulin lispro	B-Isophane insulin (NPH)	C- Lente insulin	D- Insulin glargine
Q2: Insulin preparations that contain a modifying protein (protamine) include			
A- Lente insulin	B-Insulin glargine	C- Isophane insulin (NPH)	D- :)
Q3: The insulin preparation of choice in diabetic ketoacidosis is			
A- Insulin lispro	B- Lente insulin	C- Isophane insulin (NPH)	D- Insulin glargine (lantus)
Q4: Which of the following insulin preparations is a clear solutions at neutral pH and Forms hexamers			
A- Insulin lispro	B-Regular insulin	C-Lente insulin	D- None of these
Q5: The most common complications of insulin is			
A- weight loss	B- Glucagon resistance	C- Hyperkalemia	D- Hypoglycaemia
Q6: One of the following drugs should not be mixed with other insulins in the same syringe.			
A- Insulin glargine	B- Lente insulin	C- Insulin lispro	D- Regular insulin
Q7: Longest acting insulin is			
A- Insulin glargine (lantus)	B- Insulin lispro	C- Lente insulin	D- Isophane insulin (NPH)
Q8: Insulin is a polypeptide hence:			
A- It is resistant to destruction by gastric juice	B- It is destroyed by gastric juice	C- It is not a polypeptide	D- It is metabolized immediately by cellular enzymes
Q9: One of the following drugs maintains a constant circulating insulin over 24 hr with no peak			
A- Insulin glargine	B- Insulin lispro	C- Lente insulin	D- Isophane insulin

1	2	3	4	5	6	7	8	9
A	C	A	B	D	A	A	B	A

Cases

MCQs

1. A 26-year-old woman diagnosed with type 1 diabetes started a treatment with insulin. Which of the following insulin combinations cannot be used for her condition?	2. A 24-year-old obese woman in her 26th week of pregnancy was diagnosed with gestational diabetes mellitus after a positive glucose tolerance test. Which of the following drugs would be most appropriate for the patient at this time?
A. NPH/regular insulin B. NPH / Lispro C. NPH / Aspart D. NPH/ Glargine	A. Regular insulin B. Insulin lispro C. Isophane insulin (NPH) D. Lente insulin
3. An 8-year-old girl diagnosed with type 1 diabetes began treatment with insulin. Which of the following actions on lipid metabolism most likely occurred in this patient after starting the therapy?	4. A 12-year-old boy diagnosed with type 1 diabetes started a treatment with insulin. Which of the following is an expected complication?
A. Increased lipid breakdown by the liver B. Decreased triglyceride storage in fat tissue C. Increased triglyceride synthesis D. Decreased synthesis of lipoprotein lipase E. Increased activity of hormone-sensitive lipase	A. Lipodystrophy C. Hypersensitivity Reactions B. Hypokalemia D. All of the above

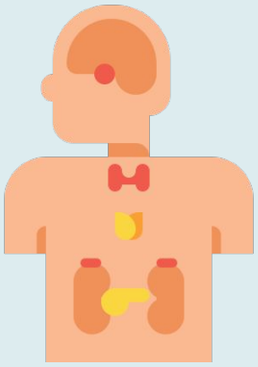
SAQ

A 35 - year - old female with diabetic ketoacidosis is admitted to the hospital with the following profile: serum glucose 412 mg/dl (22.9 mmol/L), pH 7.12, K + 4.4 mEq/L, Na + 141 mEq/L, and PO 4 2.4 mEq/L (0.77 mmol/L).
1. Mention 2 drugs that can be used for her condition and their route of administration
2. Mention the mechanism of action of the drugs mentioned on question 1
3. Mention 3 possible complications of the drugs mentioned on question 1

SAQ answers	
	1. Ultra short acting insulin (Insulin lispro I.V), short acting insulins (Humulin I.V)
	2. a) Phosphorylation of IRS-1 and IRS-2 (insulin receptor substrate) b) → binding and activating other kinases : or bind to adaptor proteins that translates insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein RAS and the MAPK system .
	3. Hypoglycemia, Hypokalemia, Weight gain as

MCQs answers		
	1	D
	2	A
	3	C
	4	D

Feedback Form



Endocrine Block

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