DRUGS FOR THE TREATMENT OF DIABETES MELLITUS

DIABETES MELLITUS

- Affects approx. 5 – 8 % of population.
- Mostly asymptomatic.
- Tendency increase with obesity.
- One of the leading cause of death by disease.
- One of the leading cause of blindness.
- One of the leading cause of renal failure.

Characteristic	Type 1 (10%)	Type 2
Onset (Age)	Usually < 30	Usually > 40
Type of onset	Abrupt	Gradual
Nutritional status	Usually thin	Usually obese
Clinical symptoms	Polydipsia, polyphagia, polyurea, Wt loss	Often asymptomatic
Ketosis	Frequent	Usually absent
Endogenous insulin	Absent	Present, but relatively ineffective
Related lipid abnormalities	Hypercholesterolemia frequent, all lipid fractions elevated in ketosis	Cholesterol & triglycerides often elevated; carbohydrate-induced hypertriglyceridemia common
Insulin therapy	Required	Required in 20 - 30% of patients
Hypoglycemic drugs	Should not be used	Clinically indicated
Diet	Mandatory with insulin	Mandatory with or without drug

EFFECTS OF INSULIN

Carbohydrate	Fat	Protein	potassium
- ↑GLUCOSE UPTAKE - ↑GLYCOGEN SYNTHESIS (↑STORAGE) - ↓GLUCONEOGENEIS (LIVER) - ↑GLYCOLYSIS (MUSCLE) - ↑ CONVERSION OF CARBOHYDRATE TO FAT (LIPOGENESIS)	↓LIPOLYSIS	↑AMINO ACID UPTAKE (PROTEIN SYTHESIS)	↑K^+ UPTAKE INTO CELLS

Insulin Deficiency – Diabetes Mellitus

- ↓Glucose uptake → Hyperglycemia → Glycosuria → Dehydration
- ↑A.A. Mobilization → ↑A.A. Plasma → Glucose
- ↑ Lipolysis → ↑Plasma FFA → Ketosis → Acidosis
- ↓ K^+ Uptake into the cells

Insulin Degradation

- Hydrolysis of the disulfide linkage between A&B chains.
- 60% liver, 40% kidney(endogenous insulin)
- 60% kidney,40% liver (exogenous insulin)
- Half-Life 5-7min (endogenous insulin)
- Delayed-release form(injected one)
- Category B (not teratogenic)Usual places for injection: upper arm, front & side parts of the thighs & the abdomen.
- Not to inject in the same place (rotate)
- Should be stored in refrigerator& warm up to room temp before use.
- Must be used within 30 days.

TYPES OF INSULIN PREPARATIONS

1. Ultra-short-acting.
2. Short-acting (Regular).
3. Intermediate-acting.
4. Long-acting.

DRUGS FOR THE TREATMENT OF DIABETES MELLITUS

1. ULTRA-SHORT-ACTING:
2. SHORT-ACTING (REGULAR):

	Short-acting (regular) insulins e.g. Humulin R, Novolin R	Ultra-Short acting insulins e.g. Lispro, aspart, glulisine
Uses	Designed to control postprandial hyperglycemia & to treat emergency diabetic ketoacidosis	Similar to regular insulin but designed to overcome the limitations of regular insulin
Physical characteristics	Clear solution at neutral pH	Clear solution at neutral pH
Chemical structure	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	30 – 45 min (S.C)	0 – 15 min (S.C)
Peak serum levels	2 – 4 hr	30 – 90 min
Duration of action	6 – 8 hr	3 – 4 hr
Usual administration	2 – 3 times/day or more	2 – 3 times / day or more

✓ *Advantages of Insulin Lispro vs Regular Insulin:*

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

3. INTERMEDIATE - ACTING INSULINS:

Isophane (NPH)(Humulin N; Novolin N, etc.):

- Turbid suspension
- Injected S.C.(Only)
- Onset of action 1 - 2 hr
- Peak serum level 5 - 7 hr
- Duration of action 13 - 18 hr
- Insulin mixtures 75/25 70/30 50/50 (NPH / Regular)

Lente insulin (Humulin L; Novolin L):

- Turbid suspension
- Mixture of 30% semilente insulin , 70% ultralente insulin
- Injected S.C. (only)
- Onset of action 1 - 3 hr
- Peak serum level 4 - 8 hr
- Duration of action 13 - 20 hr

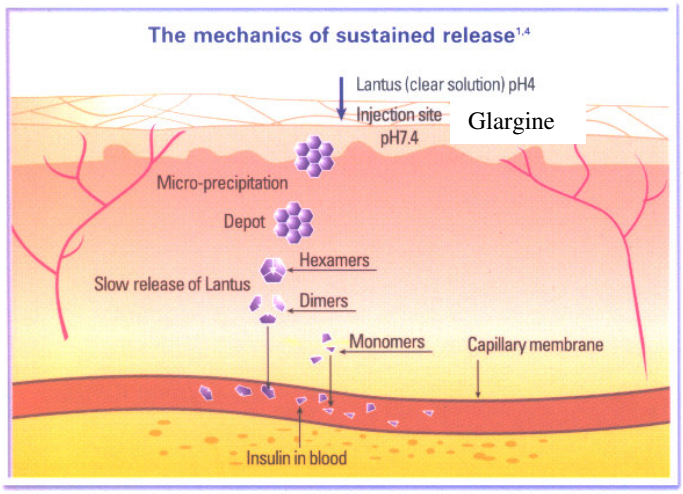
Lente and NPH insulins:

- Are roughly equivalent in biological effects.
- They are usually given once or twice a day.
- N.B: They are not used during emergencies (e.g.diabetic ketoacidosis).

4. LONG – ACTING INSULINS: e.g.Ultralente(Humulin U), glargine (Lantus)

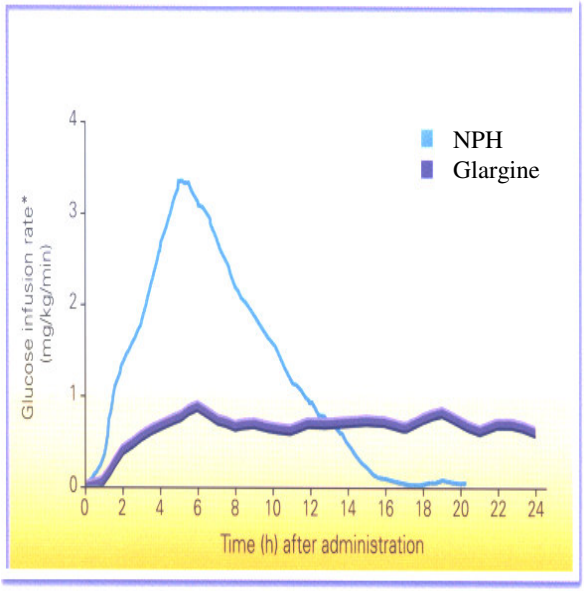
Insulin glargine:

- Onset of action 2 hr
- Absorbed less rapidly than NPH&Lente insulins.
- Duration of action upto 24 hr
- Designed to overcome the deficiencies of intermediate acting insulins



✓ *Advantages over intermediate-acting insulins:*

- Constant circulating insulin over 24hr with no pronounced peak.
- More safe than NPH&Lente insulins (reduced risk of hypoglycemia, esp.nocturnal hypoglycemia).
- Clear solution(does not require resuspention before administration).



✓ Methods of Administration:

- Insulin Syringes
- Pre-filled insulin pens
- External insulin pump

✓ Under Clinical Trials:

- Oral tablets
- Inhaled aerosol
- Intranasal, Transdermal
- Insulin Jet injectors
- Ultrasound pulses

COMPLICATIONS OF INSULIN THERAPY

1. Severe Hypoglycemia (‹ 50 mg/dl)– Life threatening
    - Overdose of insulin
    - Excessive (unusual) physical exercise
    - A meal is missed

   How it is treated ?
2. Weight gain
3. Local or systemic allergic reactions (rare)
4. Lipohypertrophy at injection sites
5. Insulin resistance (IgG anti-insulin antibodies, infections, expired insulin).
6. Hypokalemia

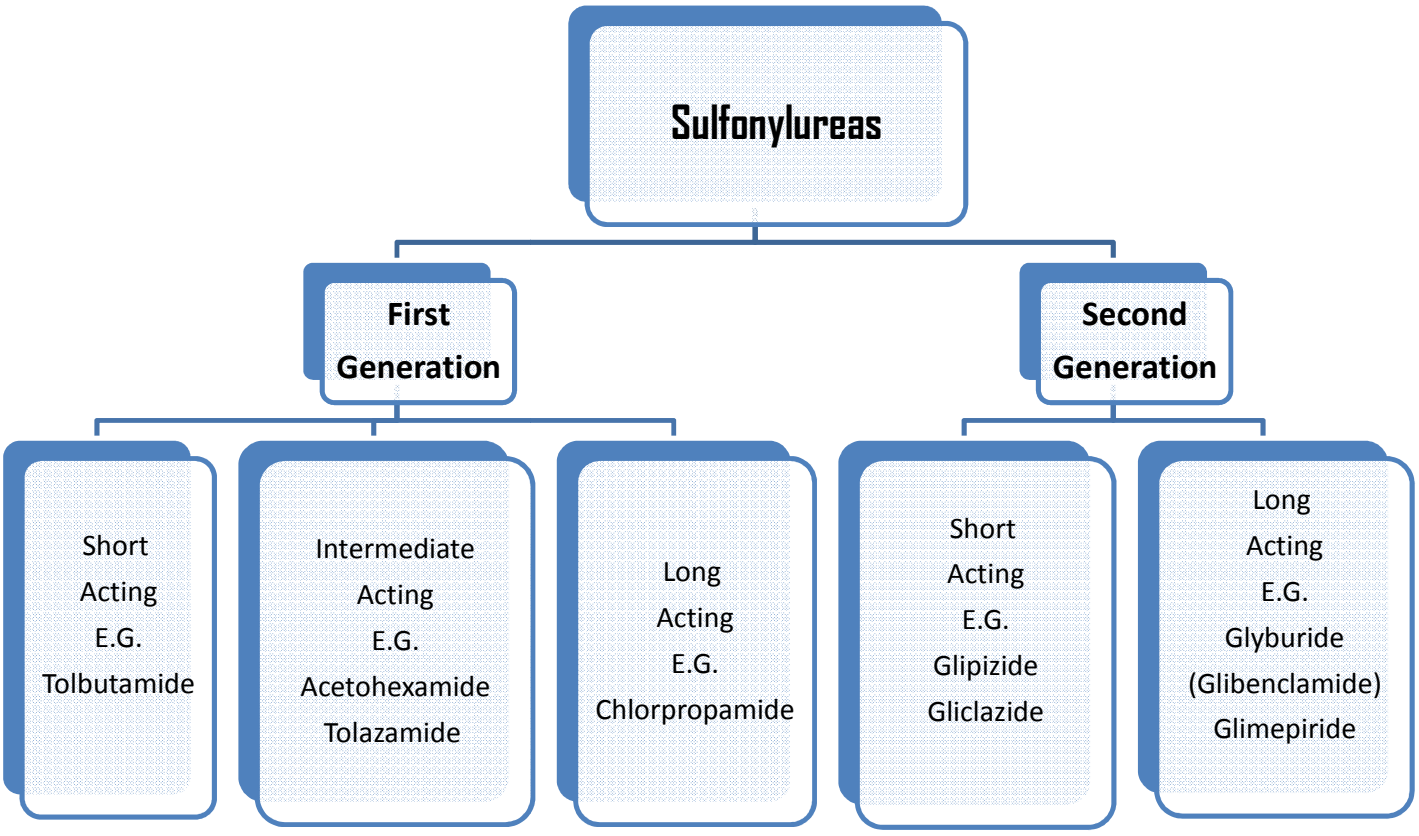
	Severe insulin reaction (Hypoglycemic Shock)	**Diabetic coma (Diabetic Ketoacidosis)**
Onset	Rapid	Slow- Over several days
Insulin	Excess	Too little
Acidosis & dehydration	No	Ketoacidosis
Signs and symps		
B.P.	Normal or elevated	Subnormal or in shock
Respiration	Normal or shallow	Deep & air hunger
Skin	Pale & Sweating	Hot & dry
CNS	Tremors, mental confusion, sometimes convulsions	General depression
Blood sugar	Lower than 70 mg/100cc	Elevated above 200 mg/100cc
Ketones	Normal	Elevated

ORAL HYPOGLYCEMICS

- All taken orally in the form of tablets.
- Pts with type II diabetes have two physiological defects:
  1. Abnormal insulin secretion.
  2. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.

ORAL ANTI-DIABETIC AGENTS

1. Sulfonylureas e.g. Tolbutamide, Glyburide. Tolazamide,Acetohexamide, Glipizide.
2. Meglitinides e.g. Repaglinide, Nateglinide.
3. Biguanides e.g. Metformin.
4. Alpha-glucosidase inhibitors e.g. Acarbose.
5. Thiazolidinediones e.g. Rosiglitazone, Pioglitazone.



FIRST GENERATION SULPHONYLUREA COMPOUNDS

	Tolbutamid short-acting	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting
Absorption	Well	Well	Slow	Well
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive*	Active +++ **	Active ++ **	Inactive **
Half-life	4 - 5 hrs	6 – 8 hrs	7 hrs	24 – 40 hrs
Duration of action	Short (6 – 8 hrs)	Intermediate (12 – 20 hrs)	Intermediate (12 – 18 hrs)	Long (20 – 60 hrs)
Excretion	Urine	Urine	Urine	Urine

- ✓ * Good for pts with renal impairment
- ✓ ** Pts with renal impairment can expect long $T_{1/2}$

SECOND GENERATION SULPHONYLUREAS COMPOUNDS

	Glipizide Short- acting	Glibenclamide (Glyburide) Long-acting	Glimepiride Long-acting
Absorption	Well	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
Half-life	3 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of action	10 – 16 hrs	12 – 24 hrs	12 – 24 hrs
Excretion	Urine	Urine	Urine

- MECHANISM OF ACTION OF SULPHONYLUREAS:

1) Release of insulin from β-cells
2) Reduction of serum glucagon concentration
3) Potentiation of insulin action on target tissues

CLINICAL USES OF SULFONYLUREAS:

- Approved as monotherapy and in combination with metformin in type 2 diabetes .
- Taken before each meal, 1-2 times / day.

SIDE EFFECTS OF SULPHONYLUREAS:

1) Nausea, vomiting, abdominal pain, diarrhea

2) Hypoglycaemia

3) Dilutional hyponatraemia & water intoxication (Chlorpropamide)

4) Disulfiram-like reaction with alcohol (Chlorpropamide)

5) Weight gain

6) Blood dyscrasias: (not common; less than 1% of patients)

   - Agranulocytosis
   - Haemolytic anaemia
   - Thrombocytopenia

7) Cholestatic obstructive jaundice (uncommon)

8) Dermatitis (Mild)

9) Muscle weakness, headache, vertigo (not common)

10) Increased cardio-vascular mortality with longterm use ??

CONTRAINDICATIONS OF SULPHONYLUREAS:

1) Type 1 DM (insulin dependent)
2) Parenchymal disease of the liver or kidney
3) Pregnancy, lactation
4) Major stress

DRUGS THAT AUGMENT THE HYPOGLYCEMIC ACTION OF SULPHONYLUREAS:

1. SULFONAMIDES
2. WARFARIN
3. SALICYLATES
4. PHENYLBUTAZONE
5. PROPRANOLOL
6. ALCOHOL
7. CHLORAMPHENICOL
8. FLUCONAZOLE

DRUGS THAT ANTAGONIZE THE HYPOGLYCEMIC ACTION OF SULPHONYLUREAS:

1. DIURETICS (THIAZIDE, FUROSEMIDE)
2. DIAZOXIDE
3. CORTICOSTEROIDS
4. ORAL CONTRACEPTIVES
5. PHENYTOIN, PHENOBARB., RIFAMPIN
6. ALCOHOL (chronic pts)

MEGLITINIDES e.g. Repaglinide, Nateglinide

PHARMACOKINETICSL:

- Taken orally
- Rapidly absorbed (Peak approx. 1hr)
- Metabolized by liver
- t1/2 = 1 hr
- Duration of action 4-5 hr

MECHANISM OF ACTION:

- Bind to the same KATP Channel as do Sulfonylureas, to cause insulin release from β-cells.

CLINICAL USE:

- Approved as monotherapy and in combination with metformin in type 2 diabetes
- Taken before each meal, 3 times / day
- Does not offer any advantage over sulfonylureas;
- Advantage: Pts. allergic to sulfur or sulfonylurea

SIDE EFFECTS:

1. Hypoglycemia
2. Wt gain (less than SUs)
3. Caution in pts with renal & hepatic impairement.

BIGUANIDES e.g. Metformin :

PHARMACOKINETICS:

- Given orally
- Not bind to plasma proteins
- Not metabolized
- Excreted unchanged in urine
- t 1/2 2 hr

MECHANISM OF ACTION:

1. Increase peripheral glucose utilization
2. Inhibits gluconeogenesis
3. Impaired absorption of glucose from the gut

ADVANTAGES OF METFORMIN OVER SUS:

1. Does not cause hypoglycemia (why ?)
2. Does not result in wt gain (why ?) (Ideal for obese pts)

INDICATIONS:

1. Obese patients with type 11 diabetes
2. Alone or in combination with sulfonylureas or meglitinides.

SIDE EFFECTS:

1. Metallic taste in the mouth
2. Gastrointestinal (anorexia, nausea, vomiting, diarrhea, abdominal discomfort)
3. Vitamin B 12 deficiency (prolonged use)
4. Lactic acidosis (rare – 01/ 30,000-exclusive in renal failure)

CONTRAINDICATIONS:

1. Hepatic impairment
2. Renal impairment
3. Alcoholism
4. Heart failure

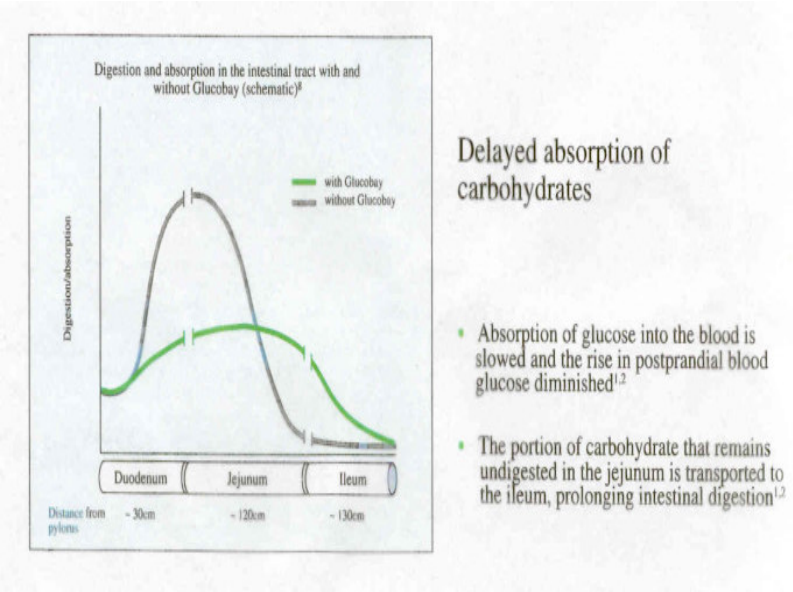
α-GLUCOSIDASE INHIBITORS e.g. Acarbose :

PHARMACOKINETICS:

- Given orally
- Not absorbed from intestine except small amount
- t1/2 3 - 7 hr
- Excreted with stool

MECHANISM OF ACTION:

- Inhibits intestinal alpha-glucosidases and delays carbohydrate absorption, reducing postprandial increase in blood glucose (designed to slow and not to prevent glucose absorption from intestine).



SIDE EFFECTS:

1. Flatulence
2. Loose stool or diarrhea
3. Abdominal pain
4. Alone does not cause hypoglycemia

INDICATIONS:

- Patients with Type 11 inadequately controlled by diet with or without other agents(SU, Metformin)
- Can be combined with insulin
- may be helpful in obese Type 11 patients (similar to metformin)

THIAZOLIDINEDIONE DERIVATIVES e.g.: Rosiglitazone , Pioglitazone:

PHARMACOKINETICS:

- 99% absorbed
- Metabolized by liver
- 99% of drug binds to plasma proteins
- Half-life 3 – 4 h
- Eliminated via the urine 64% and feces 23%

MECHANISM OF ACTION:

❖ Increase target tissue sensitivity to insulin by:
   A. reducing hepatic glucose output & increase glucose uptake & oxidation in muscles & adipose tissues.
   B. They do not cause hypoglycemia (similar to metformin and acarbose) .

INDICATIONS:

- Type 11 diabetes alone or in combination with metformin or sulfonylurea or insulin in patients resistant to insulin treatment

ADVERSE EFFECTS:

1. Mild to moderate edema
2. Wt gain
3. Headache
4. Myalgia
5. Hepatotoxicity ?
6. Alone does not cause hypoglycemia