DRUGS USED IN DIABETES MELLITUS

Classification of Diabetes

- Type 1 Diabetes
- Type 11 Diabetes
- Diabetes due to secondary causes
- Gestational Diabetes

Drugs used for diabetes

all lower blood glucose

INSULINS:

only injectable preparations at present

Other antidiabetes drugs: oral preparations

Known as oral antidiabetes drugs/

Oral hypoglycaemic drugs

Oral antidiabetes drugs

- Main drug classes can classified according to,
- (How drugs have been developed)
- Efficacy
- Safety
- Suitability
- Availability
- Cost
- Drug interactions
- New drug classes & their place in therapy

Main oral antidiabetes drug classes for type 2 diabetes

Considering the defects in type 2 diabetes

- Drugs to increase ***insulin secretion***

  1. **Sulphonylureas**

- Drugs to improve ***insulin action*** (Insulin sensitivity)

  2. **Biguanides**

Sulphonylureas: classification

1st generation

- **Tolbutamide**
- Tablet strength 500mg
- T ½ 8 hours
- 1-3 times/day
- Max. daily dose 2g
- With meals

- Chlorpropamide

2nd generation

- **Glibenclamide**
- Tablet strength 5mg
- T ½ 10 hours
- 1-2 times /day
- Max. daily dose 15mg
- With meals
- (up to10mg before breakfast >10mg add before dinner)

- *Glipizide**
- *Gliclazide**

Sulphonylureas

- Chance of hypoglycaemia with sulphonamides
- First used for diabetes in 1954
- Efficacy: very effective (good blood glucose lowering capacity)
- Potency: glibenclamide>tolbutamide
- Hypoglycaemia: glibenclamide> tolbutamide

SU: mechanism of action

Main action

- Promote insulin secretion ("secretogauge") by degranulation of beta cells of the pancreas (release of stored insulin)

- Action by closure of K channels on the beta cell membrane and facilitate Ca^{++} entry to beta cells

Other possible actions (long term effects)

- Increase insulin receptor number at target tissue
- Increase glucose uptake by muscle
- Reduced glycogenolysis

Pharmacokinetics

- Well absorbed from GIT
- Highly protein bound
- Metabolized in the liver
- Excreted by the kidneys
- Some drugs have active metabolites

Sulphonylureas: indications

- Non obese type 2 diabetes: not responding to dietary therapy

- Non obese Type 2 diabetes: presenting with a complication

  eg. a foot ulcer, UTI (together with dietary therapy)

Adverse effects

common

- ***Hypoglycaemia***

More with long t ½ drugs

Tolbutamide causes

Prolonged hypoglycaeamia

t ½ 36 hours

Weight gain

very rare

- Nausea.vomiting,diarrhoea
- Neutropenia, low platelets
- Skin rashes: ***erythema multiforme, Steven Johnson syndrome***
- Jaundice with chlorpropamide
- Disulfiram like reaction with chlorpropamide
- Liver impairment

Contraindications / cautions

- Type 1 diabetes
- Pregnancy
- Breast feeding
- Liver disease
- stressful states eg, severe infections, MI, surgery
- Hyperglycaemic emergencies (DKA & HONK)

Caution

- Renal impairment
- Elderly
  (tolbutamide has a short half life and is not excreted by the kidneys, hence is preferred to glibenclamide)

Sulphonylurea(SU) failure

- Failure to lower blood glucose with SU

  Primary failure
- If it occurs with in 1 month of starting therapy

  Secondary failure
- due to beta cell exhaustion and failure to produce insulin and insulin resistance

  Insulin therapy is recommended for both types

Tolbutamide

- Short acting
- Metabolized in the liver
- Safer in patients with renal impairment
- Safer in elderly

Chlorpropamide.

- Longer duration of action
- Risk of prolonged hypoglycaemia
- Should not be used in elderly

Glibenclamide

- Widely used
- Can be given as a single daily dose
- Started with a daily dose of 5mg in the morning before breakfast
- Max dose is 15 mg/day

Biguanides

metformin 500mg

Mechanism of action

- *Increase glucose uptake by muscle in the presence of insulin*
- *Increase* **insulin receptor number and affinity** *of target tissue*
- *Inhibition of hepatic* ***gluconeogenesis***
- *Reduced intestinal glucose absorption*
- *Reduced appetite and weight loss*

Metformin: Pharmacokinetics and indications

- Well absorbed
- Renal excretion (unchanged)

Indications

- Obese type 2 diabetes not responding to diet alone
- Obese type 2 diabetes presenting with a complication such as UTI or a foot ulcer
- Type 2 diabetes: when hypoglycaemia is a risk to life

Metformin: Adverse effects

Common

- ***Gastrointestinal disturbances***
- Anorexia , nausea, vomiting, diarrhoea
- Malabsorption
  (B12 absorption)

Start with a low dose
Immediately after meals
1-3 times /day
Max daily dose 3g (1gx3)

Rare

- ***Lactic acidosis***
  (A serious condition)
- ***Hypoglycaemia***
  (Very rare)

Metformin:

contraindications and caution

- Major organ failure (liver, heart, respiratory, renal)
- Radiological investigations with contrast (dye)
- Pregnancy & breast feeding
- Surgery (perioperative)
- Type 1 diabetes
- Hyperglycaemic emergencies

Caution

- Elderly and people with renal impairment
  Use a lower daily dose (<2g)

Comparison of

Sulphonylureas	Metformin
Weight gain	No weight gain (weight loss)
Hypo: common	Hypo: rare
GIT side effects rare	GIT side effects common
Metabolised in liver	Not metabolized
Excretion liver/renal	Renal excretion

- ***A sulphonylurea drug may be combined with metformin***
- ***Two sulphonylurea drugs should not be combined***

New oral antidiabetes drugs

- **Alpha glucosidase inhibitors** eg. acarbose

Delayed conversion of disaccharides to monosaccharides

Problems: intolerable GIT side effects

Liver toxicity (hepatitis),monitor liver function

Meglitinides: insulin secretogauges (non SU)

eg repaglinide, nateglinide

Thiozolidinediones: Improves insulin sensitivity

eg pioglitazone, rosiglitazone

Problems: Heart failure and liver failure

Insulin

- Polypeptide with 2 peptide chains
- Linked by 2 disulphide Bonds
- Metabolic activity is common to all mammalian species
- Daily secretion 30-40 units

Pharmacokinetics

- Injected because digested if swallowed
- Absorbed in to the blood inactivated in the liver & kidney.
- 10% appear in urine.
- T 1/2 is 5 min
- Peak plasma concentration is in 30-90 min

Insulin Receptors

- Bound to a receptor Tyrosine kinase on the surface of target cell.
- Insulin receptor complex enters the cell

Preparations of Insulins.

- Source of Insulin(Human,Bovine,Porcine)
- Formulation
  - Short acting
  - Intermediate acting
  - Long acting
  - Bi phasic

Short Duration Of action Insulins

- Rapid onset of action
  - Soluble Insulin
  - Insulin Lispro

Intemediate duration of action

- Isophane Insulin - A suspension with protamine

- Amorphous - Insulin zinc suspension

Longer duration of action Insulin

- Insulin Zinc suspension -Crystalline

Biphasic Insulins

- Mixture of soluble insulin & Isophane insulin
- Most commonly used ones are human Insulins
- Soluble Insulin at 10-50% of total Insulin concentration
- Remove the need for patients to mix Insulin

Indications for use of Insulin.

- Type 1 Diabetes mellitus
- Type 11 Diabetes
  - Diabetic ketoacidosis
  - Non ketotic hyper osmolar coma
  - Surgery
  - Infections
  - Pregnancy

Side effects of Insulin

- Hypoglycaemia
  - Warning signs due to Neuroglycopenia (refers to a shortage of glucose (glycopenia) in the brain, usually due to hypoglycemia.)
  - Coma ,Convulsions & Death
- Allergic reactions
- Lipoatrophy (adverse immunologic response)
- Lipohypertrophy (lipogenic properties of insulin)

Soluble Insulin

- Short duration of action
- Used 30m before meals
- 3 times a day
- Colourless.
- Is given I.V in diabetic ketoacidosis.

Insulin zinc suspensions

- Amorphous
- Crystalline

Dose of Insulins

- 100u/ml
- Total daily output is 30-40 units a day
- A dose of over 100u/day is due to noncompliance.

Advice to the patient

- Don’t skip a meal
- Signs of hypoglycaemia
- Diet planning
- Regular checkups

THANK YOU