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## DRUGS FOR GLUCOSE MANAGEMENT AND DIABETES

SUNALI MEHTA

Drugs to know are:

Actrapid HM

Humulin R , L, U

Penmix

The three principal hormones produced by the pancreas are:

Insulin: nutrient metabolism: inhibits glycogenolysis and gluconeogenesis

Glucagon: nutrient met: stimulates glycogenolysis and gluconeogenesis

Stomatostatin: inhibits all endocrine secretion from the pancreas.

Insulin and glucagons are primarily involved in the maintenance of blood glucose level

Hyperglycaemic agents:

Glucagon is primarily used to treat the conditions of hypoglycaemics where intravenous glucose cannot be administered. It is produced in the alfa cells of the islets of langerhangs in the pancreas. It raises the blood glucose level by activating glycogenolysis and gluconeogenesis. It also relaxes the smooth muscle walls of the GI tract and hence reduces the GI motility and muscle tone. Nausea and vomiting are the two main adverse effects.

Muscle relaxant property helps in endoscopic and radiographic procedures of the gut. The preparation needs to be protected from heat and light.

## Diabetes Mellitus:

It is a condition which is characterized by the amount of insulin demand and insulin availability or responsiveness.

Two common forms:

Type 1: insulin dependent

Type 2: non – insulin dependent

Gestational diabetes.

Type I : is characterized by an complete deficiency of insulin and the histological examination of the pancreas reveals that the beta islet cells of the pancreas are deficient and there is fibrosis of the islet tissue. It is an autoimmune disorder. The peak age of diagnosis is childhood and the person suffers from acute episodes of hyper and hypoglycaemia. The person is lean

Type II: relative insulin deficiency where not enough insulin is produced to meet the requirement or it is destroyed before it can be used. It can also result due to a dec in the number of insulin receptors in the peripheral tissue. Level of insulin the blood for these people may be above normal. Peak age 40. Typical body type is obese. Acute episodes of hyperglycaemia that can develop.

Long term complication include: blindness, kidney impairment, neuropathy and cardiovascular disease.

The drugs used in the treatment of this disorder is hypoglycaemic agents

1. Insulin: reduces blood glucose level by facilitating the uptake of glucose into the cells. It stimulate glycogenesis. It also affect the metabolism of proteins and fat. It helps in the uptake of amino acid into the cells and thereby facilitates protein synthesis and fat storage. Short term benefit reduce the attacks of hyperglycaemia. Long term benefits: reduce the impaired functions such as those

of the peripheral nervous system, kidney failure, visual difficulties, wound healing, susceptibility to infection and CV disease.

Adverse reaction: hypoglycaemia, lipodystrophy, allergic reactions and insulin resistance. The incidence of latter three have fallen due to the use of human form of insulin.

Peptide insulin cannot be administered orally since it will be destroyed by the proteolytic gut enzymes. Hence should be injected either via intravenous or subcutaneous routes. Regular insulin is at an acidic pH of 3.5 and is a highly soluble form of crystals of Zinc Insulin but it is more active physiologically at a neutral pH and hence is mixed with either an acetate or phosphate buffer. This is known as neutral insulin. It can be administered subcutaneous or IV. This preparation of insulin is a clear solution which on administration forms a complex of six insulin molecules called a hexamer and this needs to be broken down before it can be absorbed into the blood stream. This delays the onset of action.

To avoid the formation of these hexamers before it is injected the concentration of the Zn can be varied in the acetate buffer to produce lente insulin or by complexes of Zn insulin and protamine in phosphate buffer called isophane or NPH insulin.

Greater the concentration of Zn or protamine in the insulin preparation the more prolonged duration and delayed is the action.

Short acting or rapid acting – neutral insulin

Intermediate acting – lente or isophane

Long acting - ultralente.

Ultra rapid acting insulin – insulin lispro or insulin aspart

Lente are relatively insoluble and hence a cloudy appearance and also are in the form of solid particles in the solution form. Only administered subcutaneous and require mixing.

In the lispro and aspart the sequence of the aa at the carboxy terminal is manipulated such that there is no change in the physiological action but at the same time it does not form hexamer as a result of which it is immediately absorbed.

Insulin therapy is required in patient with type 1 whereas it maybe required only for a short period of time in type 2 or when the patient does not respond well to the oral hypoglycaemic agents.

Oral Hypoglycaemic agents:

Drugs to know:

Chlorpropamide

Glibenclamide

Glipizide

Tolbutamide

Metformin

Four categories:

Sulfonylureas: derived from the group of sulfonamide antibiotics

Biguanides

Thiazolidinedones

Meglitinides

None of these groups decrease the blood gluc level directly but they act indirectly by inc the effectiveness or by mimicking the action of the endogenous insulin. Hence these drugs can only be used in the treatment of type II and not type I.

Blood gluc value shows fasting and postprandial values on a daily basis and glycosylated hemoglobin level reveals a big picture of glucose control over a period of 8 – 12 weeks.

Sulphonylureas:

They act in three ways:

1. They stimulate the release of insulin from the pancreas
2. Inhibit the process of gluconeogenesis in the liver
3. Increase the number of receptors for insulin on the target cells.

They bind to the K channels in the pancreatic beta cells and inhibit K efflux. This results in the depolarization of the cell membrane and Ca ion influx and as a result a release of stored insulin from the beta cells.

Adverse rxn:

Hypoglycaemia, allergic skin rxn, depression of bone marrow, GI disturbances.

These should be administered with food to reduce the risk of hypoglycaemia. Combined treatment with other oral hypo or insulin can be effective rather than substituting one sulf for another.

Biguanides:

Metformin: is the only one of its kind that is available for treatment of type II  
It promotes the uptake of insulin by enhancing the binding of the insulin to its receptor and dec production of gluc in the liver.

Common side effects include drug tolerance and acidosis the later is due to the build up of lactic acid in the blood. GI disturbances such as nausea and vomiting.

Does not induce hypoglycaemic state and hence better known as a euglycaemic as it restores normal blood glucose level.

Should be taken with meals to avoid gastric disturbances. Has a slow onset hence control may take upto few weeks.

Thiazolidinediones:

Can be used as monotherapy or as an combination.

Improve the body cell sensitivity to insulin via the stimulation of the receptor, peroxisome proliferator activated receptor, in skeletal muscle , liver and fat cells.

This receptor modulates the activity of the genes programmed to reduce hyperglycaemia. These are insulin sensitizers or insulin mimics.

Side effects include: oedema, mild anaemia and wt gain. Hepatic function needs to be monitored.

Meglitinides:

Stimulates secretion of rapid short term insulin during meals. These are also known as insulin secretagogues just like sulfonalureas and are also associated with binding to the K channels.

Common adverse rxn: GI disturbances and hypoglycaemia.

Rapid onset of action and has a short duration.

Post prandial hypoglycaemic agents:

Acarbose: is a microbial compound which is a complex carbohydrate. It is used in patients where dietary control does not work, or when oral hypo don't work or are not tolerated.

This competes with the disaccharides and polysaccharides in the intestine for the binding site of the carbohydrate enzyme. As a result the carbo cannot be broken down to absorbable monosaccharide and since the absorption is delayed it delays the rise of blood gluc post prandially.

Common side effect is GI disturbance