Oral Hypoglycemics

These are useful in the treatment of type 2 DM who do not respond adequately to non-medical interventions (diet, exercise and weight loss).

Newly diagnosed Type 2s (less than 5 years) often respond well to oral agents, patients with long standing disease (often diagnosed late) often require a combination of agents with or without insulin.

The progressive decline in B-cell function often necessitates the addition of insulin at some time in Type II diabetes. Oral agents are never indicated for Type I DM.
PATHOGENESIS GENETIC FACTORS
CONSTITUTIONAL DECREASED INSULIN FACTORS SECRETION
conordance in identical twin
obesity
lipotoxicity
both parents diabetic
hypertension
Glucose toxicity of islet 50% risk to child
low physical activity cells
INSULIN RESISTANCE
Receptor & post receptor defects
INCREASED HEPATIC GLUCOSE SYNTHESIS HYPERGLYCAEMIA Impaired glucose utilisation
TYPE 2 DIABETES MELLITUS
TYPES OF DIABETES FEATURE
TYPE1DM TYPE2 DM
Frequency 10-20% 80-90% Age at onset Early (below 35) Late (after 40) Type of onset Abrupt and severe Gradual & insidious Weight Normal Obese HLA Linked to HLA DR3,4,DQ - Family history <20% About 60% Genetic locus - Chromosome 6 Pathogenesis Autoimmune destruction of Insulin resistance beta pancreatic cells Islet cell antibodies - present Decreased insulin Normal or increased insulin Clinical management Insulin & diet Diet,exercise,oral drugs,insulin Acute complications Ketoacidosis Hyperosmolar coma
SIGNS & SYMPTOMS OF DM
Insulin deficiency causes hyperglycaemia leading to glycosuria KETOACIDOSIS
Increased catabolism: – increased lipolysis(in adipose tissue) – Increased fatty acids (in plasma) – Oxidation(in liver)
Decreased anabolism: DIABETIC COMA – Osmotic diuresis – Dehydration & loss of electrolytes .
LONG TERM COMPLICATIONS OF DIABETES
MICROVASCU SORBITOL INFECTIONS

Metabolic changes Vascular changes Immune changes LAR
Lesions : aorta Like atherosclerosi ,eye slideshare.net/raghuprasada/class-oral-hypogiy

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Oral Hypoglycemics

These are useful in the treatment of type 2 DM who do not respond adequately to non-medical interventions (diet, exercise and weight loss).

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PROTEIN DEFECTIVE Gangrene in GLYCOSYLATIO PMN extremities N FUNCTION Neuropathy fungal MACROVASCU infections, bact LAR Retinopathy , Neuropathy nephropathy infections Nephropathy retinopathy .

Oral hypoglycemics Agents

Oral hypoglycemics agents that are given orally to reduce the blood glucose levels in diabetic patients

Five types of oral antidiabetic drugs are currently in use: Biguanides :metformin

Sulfonylureas: glimepiride, glyburide, tolbutamide, glibenclamide, glipizide

Meglitinides : nateglinide, repaglinide

Thiazolidinediones : pioglitazone, rosiglitazone

Alpha -glucosidase inhibitors: acarbose, miglitol .

The oral antidiabetic drugs are of value only in the treatment of patients with type 2 (NIDDM) diabetes mellitus whose condition cannot be controlled by diet alone.

These drugs may also be used with insulin in the management of some patients with diabetes mellitus, Use of an oral antidiabetic drug with insulin may decrease the insulin dosage in some individuals.

Biguanides Metformin : is the only drug of this class presently available in market

It does not cause hypoglycaemia

MOA : They increase glucose uptake and utilisation in skeletal muscle (thereby reducing insulin resistance) and reduce hepatic glucose production (gluconeogenesis).

Pharmacokinetic aspects : Metformin has a half-life of about 3 hours and is excreted unchanged in urine .

Unwanted effects : -dose-related gastrointestinal disturbances -Lactic acidosis is a rare but potentially fatal toxic effect -Long-term use may interfere with absorption of vitamin B12

Contra indications -metformin should not be given to patients with Renal failure Hepatic disease Hypoxic pulmonary disease Heart failure or shock.

Sulfonylureas 1st gen : Tolbutamide and Chlorpropamide

2nd gen. glibenclamide, glipizide, glimperide

MOA : Acts on B cells stimulating insulin secretion and thus reducing plasma glucose

Tolbutamide : half-life : 6-12 hrs P'kinetics : Orally administered, Some converted in liver to weakly active hydroxytolbutamide; some carboxylated to inactive compound. Renal excretion.

ADR : Hypoglycaemia. May decrease iodide uptake by thyroid. Contraindicated in liver failure, renal failure patients.

Glibenclamide : -half life : 18-24 hrs P'kinetics : Orally given, Some is oxidised in the liver to moderately active products and is excreted in urine; 50% is excreted unchanged in the faeces.

ADR : May cause hypoglycaemia. The active metabolite accumulates in renal failure.

Glipizide : half-life : 16-24 hrs P'kinetics : Peak plasma levels in 1 hour. Most is metabolised in the liver to inactive products, which are excreted in urine; 12% is excreted in faeces.

ADR : Causes hypoglycaemia Has diuretic action

Most sulfonylureas cross the placenta and enter breast milk; as a result, use of sulfonylureas is contraindicated in pregnancy and in breast feeding

Drug interactions : NSAIDs, MAO inhibitors, anti bacterials, and anti fungals .
Meglitinides These act, like the sulfonylureas, but they don't have sulfonylurea moiety. These include repaglinide and nateglinide
MOA : Same as sulfonylureas .
Short duration of action and a low risk of hypoglycaemia.
Given orally, rapidly metabolized by liver enzymes .
Glitazones Currently marketed thiazolidinediones: Rosiglitazone and Pioglitazone
MOA : Bind to a nuclear receptor called the peroxisome proliferator-activated receptor-γ (PPARγ), which is complexed with retinoid X receptor (RXR).
PPARγ-RXR complex bind to DNA, promoting transcription of several genes with products that are important in insulin signalling.
P'kinetics : A-Orally, highly plasma protein bound, peak plasma concentration-within 2 hrs M- liver enzymes. E- Rosiglitazone metabolites in urine, Pioglitazone metabolites in bile .
Unwanted effets : -Weight gain -fluid retention, headache, fatigue and gastrointestinal disturbances. Have also been reported. Thiazolidinediones are contraindicated in pregnant or breast-feeding women and in children.
α-Glucosidase inhibitors Acarbose : An inhibitor of intestinal α- glucosidase, is used in type 2 diabetes.
MOA : It delays carbohydrate absorption, reducing the postprandial increase in blood glucose .
Unwanted effects : flatulence, loose stools or diarrhoea, and abdominal pain and bloating.
Like metformin, it may be particularly helpful in obese type 2 patients, and it can be coadministered with metformin.
RECENT DRUGS
PEPTIDE ANALOGS Injectable Incretin mimetics (insulin secretagogues)
Molecules that fulfill criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP)
Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).
FDA APPROVED DRUGS: Exenatide (first GLP-1 agonist)
Liraglutide (a once-daily human analogue 97% homology)
Taspoglutide (phase III clinical trials with Hoffman-La Roche) Side-effects: -decreased gastric motility -nausea -weight loss .
DIPEPTIDYL PEPTIDASE-4 INHIBITORS Increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4.
Examples:
vildagliptin (Galvus) EU Approved 2008
sitagliptin (Januvia) FDA approved Oct 2006
saxagliptin (Onglyza) FDA Approved July 2009
Linagliptin (Tradjenta) FDA Approved May 2, 2011
DPP-4 inhibitors lowered haemoglobin A1C values by 0.74%, comparable to other anti-diabetic drugs.
Inhibition of DPP-4 Increases Active GLP-1 Mixed meal Intestinal GLP-1 release GLP-1 GLP-1 (7-36) active active DPP-4 DPP-4 GLP-1 inhibitor inactive Adapted from Rothenberg P, et al. Diabetes. 2000;49(suppl 1):

Overview of insulin
Pharmacokinetics Sitagliptin : Well absorbed through GIT 80% excreted unchanged in the urine half-life :8 to 14 hours Renal clearance: 388 mL/min .
INJECTABLE AMYLIN ANALOGUES **Actions:** – Slow gastric emptying – Suppress glucagon.
Pramlintide (the only clinically available amylin analogue: administered by subcutaneous injection)
Adverse effect :nausea Typical reductions in A1C values are 0.5–1.0%.
INSULIN A polypeptide hormone with two peptide chains that are connected by disulfide bonds.

Synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C peptide, both of which are secreted by the ß cells of the pancreas triggered by high blood glucose.. Insulin and glucagon regulate blood glucose levels.
ACTIONS : Controls intermediary metabolism, having actions on liver, muscle and fat.
Conserves fuel by facilitating the uptake and storage of glucose, amino acids and fats after .
Insulin structure
Insulin levels
Sources of insulin : Human insulin is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human insulin.
MOA : Acts on insulin receptors on liver cells ,fat cells and stimulates glucose transport across membrane by ATP dependent transporters like GLUT 4 &GLUT 1 .
Insulin administration : Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. It therefore is generally administered by subcutaneous injection .
TYPES OF INSULIN PREPARATIONS :
1. Rapid-acting and short-acting insulin preparations : Regular insulin, insulin lispro, insulin aspart, and insulin glulisine -these insulin preparations reach peak plasma concentration in 30-90 mins. Insulin lispro is an insulin analogue in which a lysine and a proline residue are 'switched.
2. Intermediate-acting insulin **:** Neutral protamine Hagedorn (NPH) insulin is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine Delayed absorption of the insulin because of its conjugation with protamine, **forming a less-soluble complex**
3.Long-acting insulin preparations : a. Insulin glargine b. Insulin detemir The length of time to onset is three to four hours and the maximum duration is 20 to 24 hours.
(4)Regular Human Insulin **–** A short-acting preparation – FDA approved to treat type 1 and type 2 diabetes and for hyperglycemia (abnormally high blood sugar) experienced during pregnancy. – Administered subcutaneously as with other insulins (the only preparation that also may be administered intramuscularly and intravenously) – This insulin acts within 15 to 30 minutes and lasts from one to 12 hours.
Pharmacokinetics of Insulin Destroyed in the gastrointestinal tract, and must be given parenterally-usually subcutaneously, but intravenously or occasionally intramuscularly in emergencies
Insulin should be administered 15-20 mins prior to meal Adverse reactions to insulin : -Hypoglycemia (most serious and common) -Others: weight gain, lipodystrophy (less common with human insulin), allergic reactions, and local reactions at site of injection .
New insulin preparations
Newer insulin delivery devices
INSULIN SYRINGES:Prefilled disposible syringes with regular or modified insulins
PEN DEVICES:Fountain pen like :insulin cartridges
INHALED INSULIN:Fine powder delivered through nebuliser,rapid absorption
INSULIN PUMPS:Portable infusion devices connected to subcutaneously placed cannula(continuous insulin infusion)
INSULIN PATCH-PEN: A small (two inches long, one inch wide and ¼ inch thick) plastic device is designed to be worn on the skin like a bandage .
IMPLANTABLE PUMPS:electromechanical mechanism regulates insulin delivery from percutaneously refillable reservoir Mechanical pumps,fluorocarbon propellants &osmotic pumps are also being developed
OTHER ROUTES: – Oral(liposome/impermeable polymer coating) – Rectal – Nasal – Intraperitoneal .
Alternative medicine Medicinal plants have been studied for the treatment of diabetes, however there is insufficient evidence to determine their effectiveness Examples: ⎪Cinnamon ⎪Chromium supplements ⎪Vanadyl sulfate a salt of vanadium