Episode 17 - Diabetes Medication

Pathophysiology

Imbalance between the effects of insulin and counter regulatory hormones.

Insulin deficiency	Counter-regulatory hormone excess
Type I diabetes mellitus (beta cell destruction) Pancreatic dysfunction (pancreatitis, tumour) Type II diabetes mellitus (peripheral insensitivity and beta cell exhaustion.	Corticosteroids (Cushing's syndrome) Catecholamines (phaeochromocytoma) Pregnancy (human placental lactogen, placental growth hormone)

Insulin

Insulin is a protein and the differences between the different types of insulin are simply a few amino acids; sometimes just a single amino acid. They can be classified according to whether they are of natural origin (i.e. bovine or porcine) or if they are produced using recombinant DNA technology (i.e. human insulin and all the different insulin analogues).

Classification	Speed of onset	Duration of action
Short acting	< 30 minutes	4 hours
Intermediate acting	1-2 hours	8-12 hours
Long acting	*	24 hours

Note: * The long-acting insulins are so slow to be absorbed that they don't really have a peak plasma concentration and you could visualise them as something more like a subcutaneous depot injection. For the same reason they can take two or three days to reach steady state concentrations.

Administration

To obtain diabetic control in the community there are basically three parameters that can be altered, which are the type of insulin, the amount given (i.e. the number of units) and when these injections are given. The patient may take their insulin once, twice or three times a day, may have what is called a basal bolus regime, or may be on a continuous subcutaneous insulin infusion.

Class	Name	Description
Short acting	Actrapid	Human insulin
	Novorapid	Insulin analogue
Intermediate acting *	Isophane insulin	NPH insulin (Neutral Protamine Hagedorn)
Long acting	Lantus	Insulin glargine
	Levemir	Insulin detemir

Note: * mixed with protamine to slow absorption. Sometimes mixed with short acting insulins to create formulations such as Novomix 30, the number indicating what proportion of the mixture is made up by short acting insulin. Insulin glargine forms insoluble micro-crystals once injected under the skin (due to pKa); these form a depot from which insulin is released. Insulin detemir binds to albumin with high affinity; it is gradually released as free drug over a period of time.

Perioperative management

Long acting insulin	Continue at 80% of normal dose
Intermediate acting insulins (including mixes)	Total daily dose reduced to 50%
Short acting insulins	Omitted on day of surgery

Anti-diabetic medication

Reduce glucose absorption	
Alpha-glucosidase inhibitors (Acarbose)	Alpha-glucosidase breaks down disaccharides into monosaccharides in the gut. Disaccharides are not absorbed and are metabolised by gut flora leading to bloating and diarrhoea.
Promote glucose excretion	
SGLT-2 inhibitors	Sodium glucose transporter 2 inhibitors prevent glucose reabsorption in the proximal convoluted tubule. Glucose in the urine predisposes to osmotic diuresis and urinary tract infections.

Increase insulin secretion (direct acting)	
Sulphonylureas	Direct action on the beta-cells of the pancreas to increase insulin secretion. Inhibition of potassium efflux via the potassium-ATPase active transporter (blocked by both Sulphonylureas and Meglitinide). Potassium remains in the cell, the membrane becomes depolarised and voltage gated calcium channels open. Increasing intracellular calcium leads to vesicles full of insulin binding to the cell membrane and releasing insulin into the circulation. Can lead to hypoglycaemia in a fasted patient and should be stopped on the day of surgery.
Meglitinides	
Increase insulin section (incretin receptor pathway)	
GLP-1 receptor agonists	Act via hormones called incretins. These are released by the GI tract in response to glucose and act to stimulate insulin secretion and inhibit glucagon secretion. An example of an incretin hormone is Glucagon-like peptide-1 (GLP-1). This is broken down by an enzyme called Dipeptidyl peptidase-4 (DPP-4). So the drugs of interest either mimic Glucagon-like peptide-1 or inhibit its breakdown by Dipeptidyl peptidase-4.
DPP4 inhibitors *	

Note: * In general, anything that leads to the secretion of insulin should be omitted on the day of surgery (risk of hypoglycaemia). DPP4 inhibitors are the only exception to this since they only stimulate insulin secretion when blood glucose levels are high, i.e. they rely on high levels (post-prandial) of endogenous GLP-1 in order to exert their effect.

Sensitise cells to insulin	
Biguanides (Metformin)	Increased insulin sensitivity. Unclear mechanism. Most likely gene transcription and up-regulation of cell surface and proteins that lead to an increased response to circulating insulin. Net effect is to increase glycogenesis, reduce glycogenolysis and gluconeogenesis.
Thiozolidinediones (Pioglitazone)	

Note: Metformin has been associated with an increased risk of lactic acidosis especially in the context of impaired renal function, or dehydration or exposure to other risk factors for acute kidney injury, i.e. major surgery, contrast media or nephrotoxic medicines. It is not a lactic acidosis caused by hypoxia; it is due to the fact that Metformin interferes with the way cells and mitochondria utilise glucose. Excreting the extra lactate is not usually a problem, but it becomes an issue under conditions of physiological stress.