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Diabetes medication pharmacology

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Key points

- People with Type1 Diabetes must always have a constant source of exogenous insulin, otherwise diabetic ketoacidosis (DKA) will result.
- People with Type 2 Diabetes can be managed either with diet alone, or a combination of diet and non-insulin glucose lowering drugs with or without insulin.
- Multiple formulations of insulin exist with markedly diverse pharmacokinetic profiles. These diverse preparations are used by people with diabetes in a variety of different regimens with the aim of both ensuring sufficient background insulin, and to minimise prandial hyperglycaemia. An understanding of the different formulations and regimens is required to facilitate safe perioperative use of insulin and to prevent complications from perioperative dysglycaemia.
- Insulins must be prescribed by the brand name, the word units must be written in full, and when administering, an insulin syringe must always be used.
- There are currently eight different classes of non-insulin glucose lowering medication, each with their own mechanism of action and side effects. An understanding of the pharmacology is essential to facilitate safe perioperative manipulation and to promote optimal perioperative outcomes.

Diabetes mellitus (DM) is a group of metabolic conditions characterized by hyperglycaemia. It is the most common metabolic condition in the world, and the incidence is increasing. In England, it is estimated that there are ~2.8 million people over the age of 16 who have diabetes.[1] There are several forms/causes of diabetes. These include:

(i) Type 1 diabetes (T1DM) is characterized by an absolute lack of insulin.
(ii) Type 2 diabetes mellitus (T2DM) is the most common form and is characterized by insulin resistance.
(iii) Gestational diabetes occurs during pregnancy and is associated with conditions including pre-eclampsia, neonatal hypoglycaemia, and fetal abnormality.
(iv) Genetic defects of β-cell function (e.g. maturity-onset diabetes of the young).
(v) Endocrinopathies (e.g. Cushing syndrome and phaeochromocytoma).
(vi) Pancreatic disease (e.g. cystic fibrosis and chronic pancreatitis).
(vii) Drugs (e.g. glucocorticoids and β-adrenergic agonists).[2]

The terms 'insulin dependent' and 'non-insulin dependent', or 'juvenile-onset' or 'maturity-onset diabetes' are no longer used. This is because a large number of people with T2DM require insulin to maintain glycaemic control, and there are also an increasing number of children (who are often obese) who have T2DM. Thus the terms 'Type 1 DM', 'Type 2 DM', and 'Type 2 DM on insulin', are now preferred.

Unless the patient's diabetes can be treated with diet, the patient will require medication to control the hyperglycaemia.

In the last 30 years, insulin pharmacology has been revolutionized by the introduction of recombinant DNA

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technology and genetically engineered human insulin, which has replaced the animal-derived insulin preparations. In more recent years, the human insulins produced by recombinant DNA technology, have been further modified by subtle molecular changes to produce insulins that have different systemic absorption from the s.c. site of injection. These are known as insulin analogues. As these biological analogues come off patent, generic drugs are being marketed. These biological generic drugs (which are known as 'biosimilars') are not identical in their purity to the initial analogue preparation, and so to be licensed need to go through safety and comparative studies. These studies have not demonstrated clinically important pharmacokinetic or pharmacodynamic differences between the biosimilar and the original analogue preparation. In 2015, Abasaglar, the first biosimilar, was licensed, which is the biosimilar of insulin glargine, a long-acting insulin analogue.

There are currently eight different classes of non-insulin glucose-lowering agents,[3] with the majority being introduced in the last 20 years. The term 'oral hypoglycaemic agents' to describe the non-insulin glucose-lowering drugs has been rendered obsolete, as the relatively new glucagon like peptide-1 analogues (GLP-1 analogues) are peptides, and thus need to be injected.

Patients with diabetes require surgery more often than the general population, and recent studies suggest that ~15% of the surgical population has diabetes. Anaesthetists need to have an understanding of the pharmacology of these agents to allow the safe use and modification of the diabetes medication during the surgical period.[4,5]

Insulin

Insulin is a peptide hormone produced by the β-cells in the pancreas. Within vertebrates the amino acid sequence is strongly conserved. Bovine insulin differs to human insulin by only three amino acids, whilst in porcine insulin the difference from human insulin is only one amino acid. Most patients are now on human insulin produced by recombinant DNA technology.

There are many types of insulin commercially available. Insulins can be classified by:

(i) The speed of onset and length of action after s.c. injection (i.e. short-acting insulin or background insulin).
(ii) The type of the insulin (i.e. bovine, porcine, or obtained from human insulin using recombinant DNA technology).
(iii) Whether the preparation contains a single type of insulin or a mixture of different insulins.

Table 1 summarizes the different insulin preparations and their pharmacokinetics.

The different types of insulin

Short-acting insulins

There are three types of short acting insulin:

(i) Very rapid-acting insulin analogues.
(ii) Human soluble insulin.
(iii) Animal soluble insulin.

The short-acting insulins are usually given to cover the glucose excursion associated with meals (prandial insulin) as part of a basal bolus regimen. The dose can be adjusted according to the size of the meal, the amount of carbohydrate in the meal, the current glucose reading, and the planned activity levels. Naturally occurring short-acting insulin, be it of human or animal origin, is known as soluble insulin.

Very rapid-acting insulin analogues

Examples: insulin aspart (Novorapid), insulin lispro (Humalog), insulin glulisine (Apidra).

Very rapid-acting insulin analogues have had a small number of amino acid substitutions made to the human insulin molecule that allow them to be absorbed at a faster rate than human insulin when injected s.c. Their onset of action is within 10–15 min of initial s.c. injection, and they have a peak of action within an hour and last for up to 4 h. They are usually given to cover the glucose excursion associated with meals (prandial insulin) as part of a basal bolus regimen. The rapid onset of action means that they can be administered immediately before or within 30 min of a meal.

Owing to these pharmacokinetic properties, these are the insulins that the Joint British Diabetes Societies (JBDS) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) now recommend to treat transient hyperglycaemia in the surgical patient.[4,5]

Human soluble insulin

Examples: Actrapid; Humulin S; Insuman rapid (Human Insulin rDNA).

Human soluble insulins start working within half an hour of s.c. injection and last for between 4 and 8 h. Even though they are an exact clone of human insulin their use is declining. This is because of their slow onset of action after s.c. administration. If they are administered immediately before a meal, patients will be prone to postprandial hyperglycaemia owing to the length of time to reach peak action.

These are the insulins that are recommended to be used in the fixed rate and variable rate i.v. insulin infusions. To reduce the incidence of error, it is recommended that the insulin is administered via a commercially prepared prefilled syringe with a concentration of 1 unit/ml.[6]

Background insulins

There are two types of background human insulin:

(i) Intermediate-acting insulin, also known as NPH (Neutral Protamine Hagedorn [NPH]).
(ii) Long-acting insulin analogues.

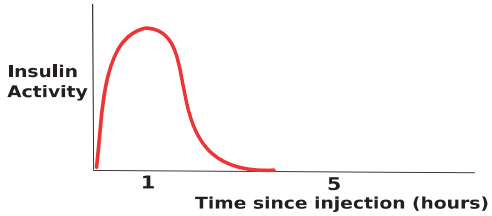
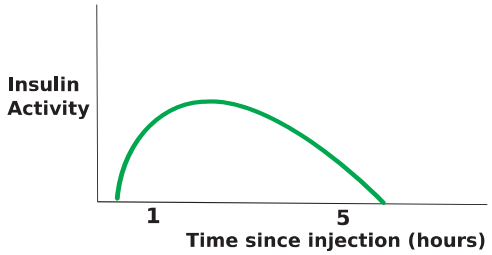
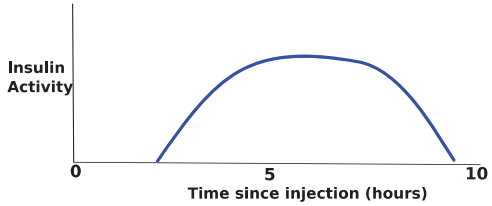
These insulins are designed to ensure a steady systemic insulin concentration, to ensure that insulin is constantly acting and to promote continuous cellular glucose uptake. The administration of these agents averts the use of fatty acids as a cellular energy substrate and thus prevents subsequent diabetic ketoacidosis (DKA). There is little to choose between 'old' NPH insulin and the 'new' longer acting insulin analogues in terms of glycated haemoglobin (HbA1c) reduction. However, there are suggestions that the rates of severe hypoglycaemia (i.e. requiring help from a third party) are lower with the long-acting analogue insulins. The newer long-acting insulin analogues are significantly more expensive than NPH.

NPH insulin/intermediate-acting insulin

Examples: Insulatard (NPH Insulin), Humulin I (Isophane insulin); Insuman basal (Isophane insulin).

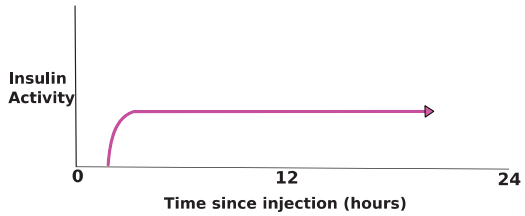
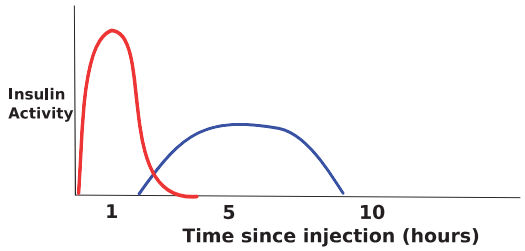
With the addition of the protamine molecule, these insulins have delayed absorption and are clinically effective 90–120 min after s.c. injection, and exert their effect for 8–10 h. These

Table 1 Summary of different types of insulin and their pharmacokinetic profiles

Type of insulin	Onset (min)	Peak activity	Duration	Pharmacokinetic profile	Clinical use
• *Rapid-acting analogue insulins*, e.g. • Novorapid (aspart) • Humalog (lispro) • Apidra (glulisine)	10 min	15 min to 1 h	3–4 h		• Bolus part of basal bolus regimen • Bolus part of twice daily separate injections (rarely used in this combination) • CSIIs pump therapy
• *Short-acting soluble human insulins*, e.g. • Actrapid • Humulin S • Velosulin	30 min	1–3 h	6–8 h		• Bolus part of basal bolus regimen • Variable rate and fixed rate i.v. insulin infusions
• *Short-acting animal (Bovine or Porcine)*, e.g. • Hypurin	30 min	Within 60 min	6–8 h		Reduced use in 21st century
• *NPH insulin/Intermediate-acting insulin*, e.g. • Humulin I • Insultard • Hypurin (Bovine or Porcine) Isophane	120 min	4–6 h	8–10 h		• Basal part of twice daily separate injections • Basal part of basal bolus regimen—can be given once or twice in this regimen
• *Long-acting analogue insulins*, e.g. • Levemir (detemir)	120 min	No peak	18–24 h		• Once daily regimen for T2DM • Part of basal bolus regimen

(continued)

Table 1. (continued)

Type of insulin	Onset (min)	Peak activity	Duration	Pharmacokinetic profile	Clinical use
• Lantus (glargine) • Tresiba (degludec)					
• *Biphasic insulin* (Combinations of either rapid-acting or short-acting soluble with an intermediate-acting insulin), e.g. • Humalog Mix 25 or Mix 50 • Humulin M3 • Insuman comb 15, comb 25 • NovoMix 30	As per components	Two peaks	As per components		Twice daily regimen, although occasionally given three times per day

insulins are commercially available either alone or in combination with either a rapid acting (e.g. NovoMix 30), or a soluble insulin (e.g. Humulin M3).

Human biphasic/mixed insulins

Examples: NovoMix 30, Humulin M3, Insuman Comb 25.

There are some commercial preparations of premixed intermediate- with a short-acting insulin. The short-acting insulin may be either a soluble insulin or a very rapid-acting insulin analogue. The number in these insulin names refers to the proportion of short-acting insulin in the combination (e.g. NovoMix 30 comprises 30% Insulin aspart (rapid-acting analogue) and 70% Insulin aspart complexed with protamine (intermediate-acting). These mixed insulins are usually given twice daily, first before breakfast and second before the evening meal. The breakfast dose allows the short-acting insulin to cover the increase in blood glucose associated with breakfast, with the intermediate-acting insulin covering the increasing glucose that would be associated with lunch. The second dose is usually taken with the evening meal, with the short-acting insulin covering the increasing glucose concentration associated with the evening meal and the intermediate insulin covering the overnight period.

Long-acting insulin analogues

Examples: insulin glargine (Lantus), insulin detemir (Levemir), and insulin degludec (Tresiba).

Insulin glargine was the first of these long-acting analogues and became available in 2003, whilst degludec only became available in 2013. These insulins have a very long duration of action—between 18 and 36 h. They take 2–3 days to reach a steady state. They are usually injected once or twice a day. They have relatively 'flat' profiles, and often described as 'peakless'.

Animal insulin

Example of short-acting (soluble) animal insulins: Hypurin neutral (bovine or porcine).

Example of intermediate-acting animal insulin: Hypurin bovine protamine zinc; Hypurin isophane (bovine or porcine).

Examples of mixed animal insulins: Hypurin 30/70 mix (porcine).

The number of patients on animal insulin (bovine, porcine) is diminishing. These are available as soluble (short-acting) or isophane (intermediate-acting) insulin. These are extracted from the pancreas of slaughtered animals. It used to take 2 tons of animal pancreases to produce 200 g of purified insulin. Animal insulin was the initial type of insulin after insulin was identified in the 1920s. With the advent of human insulins in the 1980s, animal insulin is now rarely used. The few patients who have continued to use it, do so because of patients' fear of hypoglycaemic unawareness on human insulins, but this fear has never been substantiated. Hypoglycaemic unawareness is the loss of symptoms of sympathetic overdrive (e.g. sweating, hunger, shaking, palpatations) when glucose levels drop. In people without diabetes, or where the diabetes is well controlled, symptoms often start to occur when glucose concentrations decline to approximately <3.8 mmol litre^{-1}, although it is very person specific. Hypoglycaemic unawareness most frequently occurs in those who have long-standing insulin-treated diabetes.

Many people on these animal insulins will be on mixtures twice a day. They have essentially the same pharmacokinetic properties as human insulin, but are far more immunogenic, and are subsequently associated with immune-mediated lipohypertrophy and lipoatrophy.

Insulin regimens

There are many different regimes depending on the need of the patient, ranging from one injection a day to up to five injections a day. The idea is to try to mimic the normal physiological concentrations of insulin. They are displayed graphically in Figures 1–4.

The different types of insulins can be given in any different combination.

Commonly used regimens:

(i) Once daily.
(ii) Twice daily.
(iii) Basal bolus.
(iv) Three times per day regimen.
(v) Continuous s.c. insulin infusions (CSIIs).

Once daily

This is almost always used in people with T2DM where the individual uses a once daily long-acting or intermediate-acting insulin at night in addition to their oral medication to overcome the high hyperglycaemia associated with inappropriate hepatic gluconeogenesis (see Fig. 1).

Twice daily

This is a very commonly used regimen in both T1DM and T2DM where a premixed insulin is injected at breakfast and evening meal (see Fig. 2).

Basal bolus

Four injections a day regimen is also called the basal bolus. This is composed of a longer acting either intermediate- or long-acting insulin analogue given once daily, most frequently at night. The additional three doses are normally composed of a very rapid-acting insulin analogue given at the time of the meal (however, some patients may use soluble). The basal dose usually equates to ~50% of the total daily insulin dose (see Fig. 3). Occasionally, the long-acting or intermediate insulin is split to be given 12 h apart; therefore the individual gives themselves five injections a day.

Three times per day

Although rarely used, this is the use of a premixed insulin given with each meal.

Continuous s.c. insulin infusions (CSII)

CSIIs ('pumps') are becoming more frequent. The UK National Institute for Health and Care Excellence guidelines[7] state that for individuals with T1DM aged >12 yr, pumps are recommended as a treatment option for those attempting to achieve target HbA1c concentrations <69 mmol mol^{-1} (8.5%), but experience disabling hypoglycaemia with multiple daily injections despite intensive education. An insulin pump delivers a fixed hourly basal rate of a very rapid-acting insulin analogue. This rate can be changed on an hourly basis. The individual gives themselves bolus doses to cover their carbohydrate intake during individual meals or snacks (see Fig. 4).

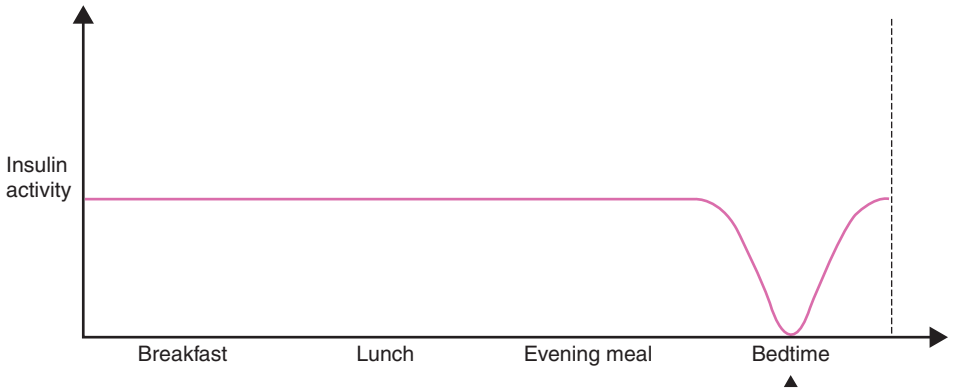


Fig 1 Insulin activity profile with a once daily injection of long-acting insulin.

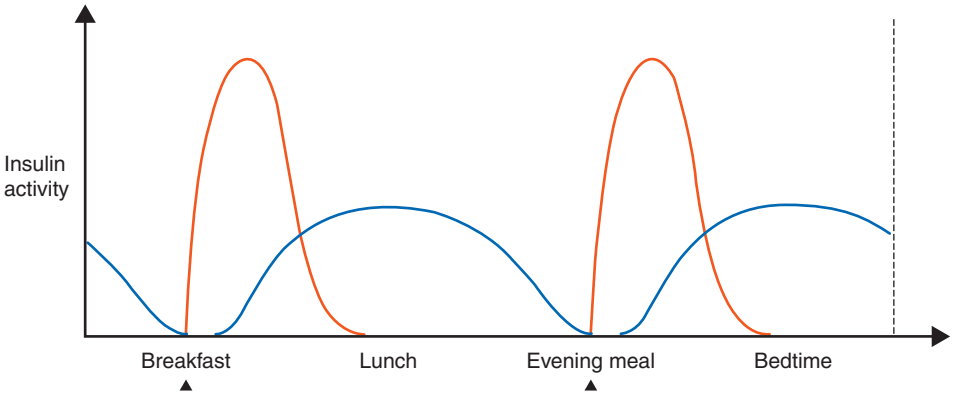


Fig 2 Insulin activity profile with twice daily injection of mixed (biphasic) insulin.

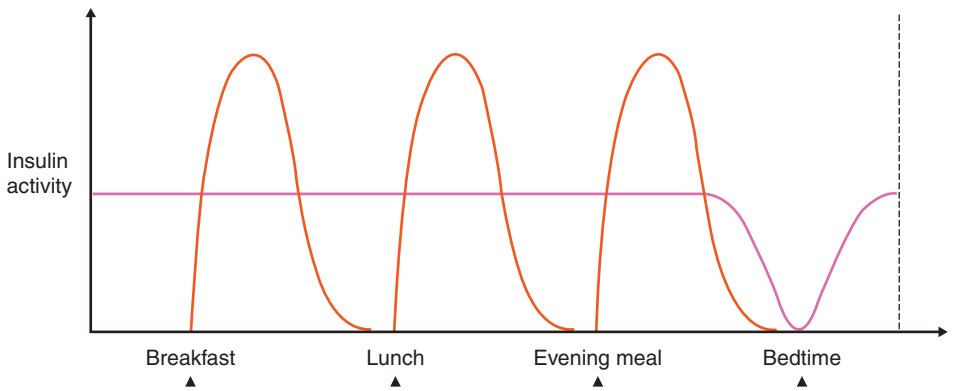


Fig 3 Insulin activity profile using a 'basal bolus' regimen.

A pump should only be used with close collaboration between the patient and the specialist diabetes team.

Inhaled insulin

Administration of insulin via the inhaled route has been difficult to achieve. The first inhaled insulin, Exubera (Pfizer Ltd), was withdrawn within a few months of launch—partly because of very poor sales, but also because of a spike in lung cancers being reported in users of the drug.[8] Newer inhaled insulins are in development and the first of these, 'Afrezza', was launched in the USA in 2015. There remain many challenges with inhaled insulins; these include: the risk of inhaling a growth factor onto a thin epithelium; the difficulty of prescribing in 'milligrams' not 'units'; and unpredictable absorption in lung disease. Whether or not this route of administration becomes viable remains to be seen.

Safe use of insulin

Whilst insulin has the potential to be a life-saving drug, its prescription and administration, and its subsequent use is associated with iatrogenic harm. Consequently, the national patient

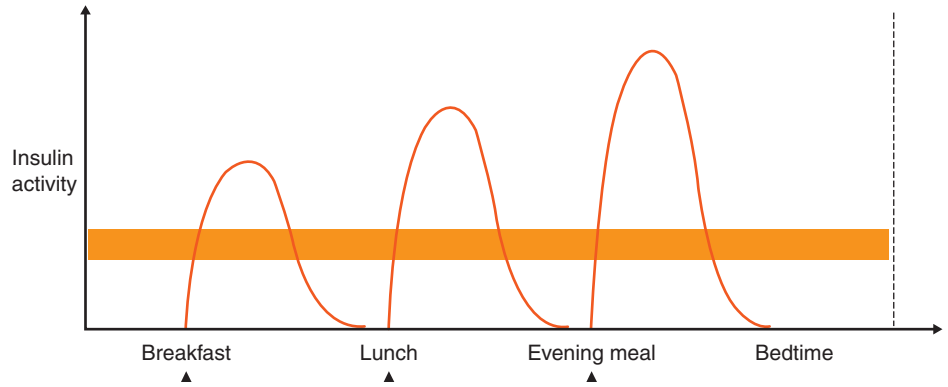


Fig 4 Insulin activity profile using a CSII. Width of CSII activity shows programmable range of basal infusion. Boluses can be adjusted to carbohydrate load of individual meals.

safety agency issued specific guidance to improve its safety in 2010.[6] The guidance included the following facts:

- All regular and single insulin (bolus) doses are measured and administered using an insulin syringe or commercial insulin pen device. I.V. syringes must never be used for insulin administration.
- The term 'units' is used in all contexts. Abbreviations, such as 'U' or 'IU', are never used.
- An insulin syringe must always be used to measure and prepare insulin for an i.v. infusion. Insulin infusions are administered in 50 ml i.v. syringes or larger infusion bags. Consideration should be given to the supply and use of ready to administer infusion products (e.g. prefilled syringes of fast-acting insulin 50 units in 50 ml 0.9% sodium chloride solution).
- Policies and procedures for the preparation and administration of insulin and insulin infusions in clinical areas are reviewed to ensure compliance with the above.

Additionally, it is vital that the insulin is prescribed by the brand name rather than the generic name. Furthermore, newer formulations of insulin are available that have different concentrations. Previously, the concentration was 100 units per ml, but insulins are now available with concentrations 200 units per ml; 300 units per ml and 500 units per ml in an attempt to help those who require large doses because of their extreme insulin resistance. Care needs to be taken to ensure that the correct dose is given when prescribing and administering these concentrated formulations. It is essential that insulin is never withheld from a patient with T1DM, otherwise DKA will ensue.

The non-insulin glucose-lowering drugs

There are currently eight different classes of non-insulin glucose-lowering drugs. These are:

(i) Sulphonylureas.
(ii) Meglitinides.
(iii) Intestinal alpha-glucosidase inhibitors.
(iv) Sodium-glucose linked transporter inhibitors (SGLT-2 inhibitors).
(v) Biguanides.
(vi) Thiazolidinediones.
(vii) Incretin mimetics/GLP-1 analogues.
(viii) The gliptins/dipeptidyl peptase-4 inhibitors (DPP4 inhibitors).

Essentially, these drugs work via four broad mechanisms:

(i) Increase release of endogenous insulin and cause a genuine reduction in the blood glucose (the sulphonylureas and meglitinides).
(ii) Affecting gastro-intestinal absorption and renal reabsorption of glucose (intestinal alpha-glucosidase inhibitors and the SGLT-2 inhibitors).
(iii) Drugs that alter effector site sensitivity to endogenous insulin and reduce gluconeogenesis/glycogenolysis or endogenous metabolism (metformin and the thiazolidinediones).
(iv) Drugs acting on the incretin pathway (GLP-1 analogues and the DPP4 inhibitors).

It is vital to note that only the sulphonylureas and meglitinides are associated with hypoglycaemia in the starved state, whilst the others are not. Thus the sulphonylureas and meglitinides should always be omitted in the perioperative period for this reason.

Sulphonylureas

Examples: glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide.

Sulphonylureas are insulin secretagogues and have been in the armamentarium of the diabetologist since the 1950s. They act by binding on the sulphonylurea receptor in the pancreatic β-cell, closing K_{ATP} channels, which depolarizes the β-cell and causes an influx of calcium. This ultimately leads to exocytosis of insulin-containing vesicles and an increase in peripheral insulin concentration. The maximum HbA1c reduction is up to 13–14 mmol mol^{-1} (1.5%).

The sulphonylureas rely on adequate β-cell function. Additionally, because of the increase in insulin secretion there is the risk of hypoglycaemia in the starved state. There are data to show that the rate of severe hypoglycaemia (i.e. needing third party assistance) for those on sulphonylureas is 0.1 per patient year.[9]

Sulfonylureas can have a very long half-life and some are renally excreted, therefore their use in the elderly and in patients with renal impairment is discouraged. The older agents, e.g. glibenclamide (half-life ~10 h), should no longer be prescribed because of this increased risk, whilst the short-acting and hepatic metabolized gliclazide is considered safer.

Sulphonylureas are widely used as second-line agents after metformin. This is because they are cheap and effective. However, as there is now evidence that the long-term use of

sulphonylureas is associated with deterioration of glycaemic control, weight gain, and increased risk of cardiovascular harm, other drugs are now advocated as second-line agents.[10]

Meglitinides

Examples: nateglinide, repaglinide.

These agents are short-acting insulin secretagogues. They work in a similar manner to sulphonylureas but are rarely used because they are short acting and thus require more frequent dosing. They have a more rapid onset and shorter duration of action than the sulphonylureas, which could have beneficial effects on decreasing late hypoglycaemia. Furthermore, repaglinide is non-renally excreted.[11]

Intestinal alpha-glucosidase inhibitors

Examples: Acarbose.

The human gut is not designed to absorb disaccharides such as sucrose and therefore an enzyme in the brush border called alpha-glucosidase cleaves the disaccharides into its component monosaccharides, which can then easily be absorbed. Inhibition of this enzyme inhibits the absorption of monosaccharides, therefore limiting the rate of rise of plasma glucose concentrations and reducing the total quantity of carbohydrate absorbed. Acarbose also inhibits pancreatic alpha-amylase, which hydrolyses complex carbohydrates into oligosaccharides. The HbA1c reduction achieved with acarbose is limited, about 8 mmol mol^{-1} (0.75%).

Acarbose can be used in combination with sulphonylureas, metformin, or insulin. Its use is however limited by its gastrointestinal side-effects. The flora that inhabit the large bowel lumen ferment the carbohydrate load, resulting in the common side-effects of bloating, diarrhoea, abdominal pain, and nausea. It is for this reason, therefore, that the dose of the drug must be built up gradually. It is contraindicated in those individuals with inflammatory bowel disease or history of previous abdominal surgery.

Sodium-glucose transporter 2 inhibitors

Examples: canagliflozin, dapagliflozin, empagliflozin.

Glucose is filtered freely through the kidneys at about 180 g day^{-1}. Normally, very little glucose is lost in the urine because it is actively reabsorbed in the proximal convoluted renal tubule by a transport mechanism linking sodium and glucose, SGLT2. This actively reabsorbs almost all the glucose that is filtered.

The SGLT2 inhibitors are a class of drug which prevent glucose reabsorption from the proximal convoluted tubules in an insulin-independent manner and give rise to the osmotic symptoms of uncontrolled diabetes: polyuria, dehydration, subsequent polydipsia, and candidiasis. They result in the loss of several grams of glucose in the urine every 24 h. There is a subsequent reduction in HbA1c of about 11 mmol mol^{-1}. They are also associated with a modest weight loss, as well as a reduction in cardiovascular mortality.[12] Because they work independently of insulin there are currently studies looking at the use of this drug in people with T1DM.

Although the risk of hypoglycaemia in the starved state is low, it is now advised that these drugs are stopped before surgery, as there have sporadic cases of DKA that have been attributed to the SGLT2 inhibitors.[13]

Biguanides

Example: metformin.

Metformin is the biguanide that is advocated by several international guidelines as the first-line treatment of people with T2DM.[3] This is because until recently, it was the only oral hypoglycaemic agent that had evidence of cardiovascular benefit.

Metformin will only work when there is circulating insulin present and it can be used in combination with other oral agents or insulin. It is one of the few oral glucose-lowering agents which is weight neutral, and the maximum HbA1c reduction is most studies is up to 13 or 14 mmol mol^{-1} (1.5%).

The use of metformin was first described in animals in the 1920s and was eventually licensed in Europe for use in humans in the late 1950s. Despite this long history of use, the exact mechanism of action of metformin remains elusive, although several mechanisms have been proposed.

Normally, in the fed state, there is suppression of endogenous hepatic gluconeogenesis owing to activation of adenosine monophosphate (AMP)-activated protein kinase. However, in T2DM there is a failure to suppress hepatic gluconeogenesis in the fed state, leading to inappropriate gluconeogenesis in the face of hyperglycaemia. Metformin reactivates hepatic AMP kinase and inhibits glucagon signalling, leading to a reduction in glycogenolysis and endogenous glucose production. This is important because the predominant action of metformin is not to lower blood glucose but to stop glucose from increasing.

Metformin also has an 'acarbose-like' action. It inhibits intestinal disaccharidase, which leads to a delay in absorption of monosaccharides and a reduction in the rate of increase of blood glucose. The resultant disaccharide load to the large bowel and subsequent micro-organism fermentation causes many of the gastrointestinal side-effects of metformin, including nausea, diarrhoea, bloating, and wind. Normally, the gastrointestinal upset does resolve; however, should it continue to be a problem then the use of modified release metformin has been shown to reduce the rate of incidence of gastrointestinal side-effects by 50%.

Metformin has also been shown to work by increasing insulin receptor expression and tyrosine kinase activity, thereby increasing insulin sensitivity. This results in a reduction of blood glucose but this effect is relatively minor compared with the effect on suppression of hepatic gluconeogenesis. The increase in insulin sensitivity can be seen in patients treated with both insulin and metformin who need to stop their metformin; the dose of insulin rapidly increases by between 25 and 35%, showing the insulin-sparing effect of the drug.

The feared complication of lactic acidosis is rare and most frequently occurs in patients who have contraindications to the use of metformin (e.g. renal and severe heart failure with low peripheral perfusion).[14] It is postulated that it is not the metformin that causes the lactic acidosis but the associated comorbidity. The dose of metformin should be reviewed if the eGFR <45 ml/min/1.73 m^2 and should be stopped if the eGFR is <30 ml/min/1.73 m^2.

The summary of product characteristics for metformin[15] suggests that that it should be stopped 48 h before surgery and the administration of iodinated contrast owing to the fear of the metabolic complications of lactic acidosis and AKI. It is now appreciated that this advice may deny many patients the benefits of glycaemic control that can be achieved with the use of metformin, as metformin is not as toxic as once thought.

In the perioperative period, the fact that metformin does not cause hypoglycaemia and is safer than previously thought allows for the JBDS and the AAGBI to recommend its continuation in elective surgery with short fasting times, as long as other risk factors for acute kidney injury are not present (e.g. the use of contrast medium, or other nephrotoxic agents).[4,5] The anaesthetic technique must be renoprotective (e.g. maintain normal blood pressure, maintain normovolaemia, and avoid other potential nephrotoxins).

Thiazolidinediones

Examples: pioglitazone.

The thiazolidinediones act on the peroxisome proliferator-activated receptor-γ, a transcription factor altering multiple genes that are involved in glucose and other substrate metabolism. They increase the sensitivity of naturally released insulin, and so again the risk of hypoglycaemia in the starved state is low.

The use of this class of drug has been severely limited over the last few years owing to the development of potential complications including increased risk of cardiovascular death, macular oedema, and bladder cancer.[16–19] The use of this class of drug is reducing, with only pioglitazone now available in the UK.

Pioglitazone works very slowly and needs to be given for at least 4–6 months for maximum benefit. It is most frequently used in combination with other agents, and the overall improvement in control is modest at 8–11 mmol mol^{-1} (0.75–1%).

The incretin pathway

Incretin hormones, such as glucagon-like peptide-1, are secreted from the gastrointestinal tract and cause a glucose-dependent increase in the secretion of insulin from β-cells. GLP-1 is produced by the L cells of the upper GI tract in response to glucose in the gut lumen. It has multiple effects including:

(i) Enhancing glucose dependent insulin secretion from β-cells.
(ii) Inhibits glucagon secretion from α-cells.
(iii) Reduces gastric emptying, slowing the rise in postprandial glucose.
(iv) Promotes satiety and reduces appetite.

People with T2DM have very low concentrations of GLP-1 compared with those without the condition.[18]

Endogenous GLP-1 has a circulating half-life of 2 min because it is broken down by an endogenous circulating enzyme called DPP-4. Greater understanding of this pathway has led to two new drug classes to treat diabetes; the GLP-1 analogues and the DPP-4 inhibitors (see Fig. 5). The overall HbA1c reduction with both these classes of drug is in the region of 11 mmol mol^{-1} (1%). They are frequently used in combination with many other medications, such as metformin, sulphonylureas, and insulin. Both GLP-1 analogues and DPP-4 inhibitors are currently contraindicated in renal failure. The gastric emptying rate may be significantly prolonged, and has been reported to nearly double. This may have important implications for the choice of anaesthesia and preoperative fasting times.[19]

Glucagon-like peptide-1 (GLP)-1 analogues

Examples: dulaglutide, exenatide, liraglutide, lixisenatide.

These drugs are peptides and thus must be administered by the s.c. route to avoid degradation by intestinal peptidases. These GLP-1 analogues are resistant to degradation by DPP-4, and thus have a longer half-life than endogenous GLP-1. The fact that exenatide can be given by weekly s.c. injection as an extended release form has the potential to aid in patient

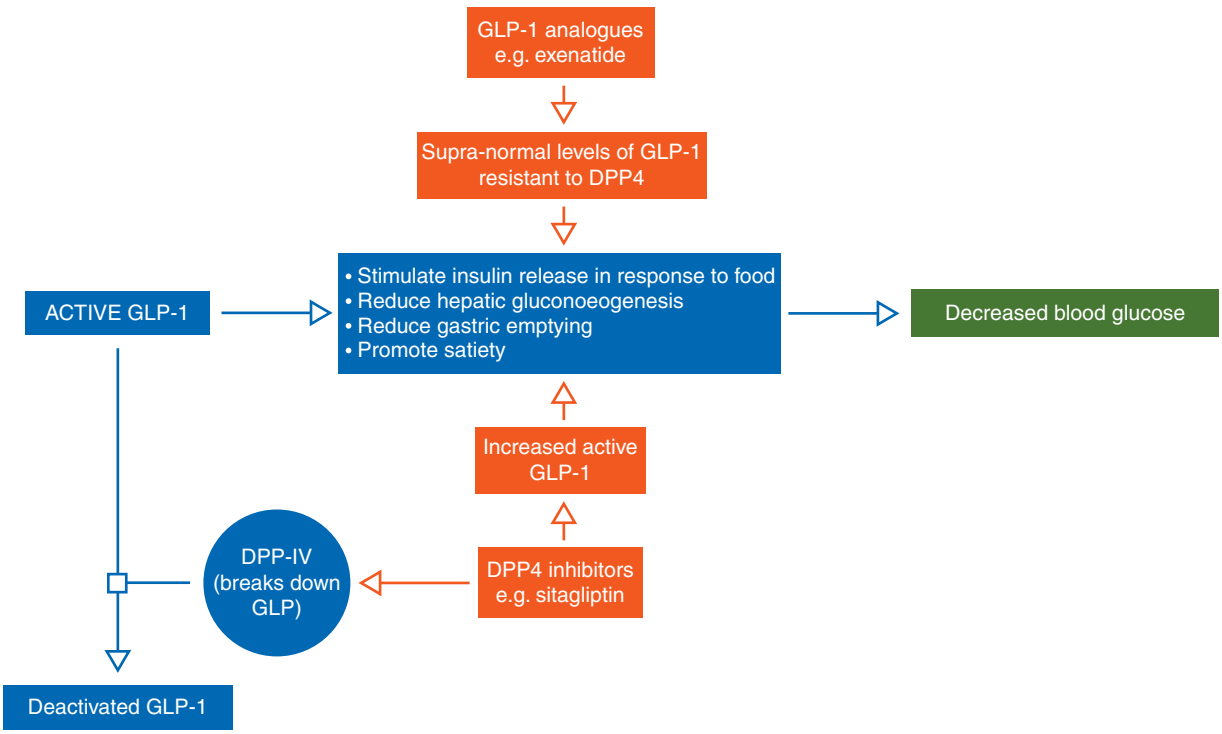


Fig 5 Pharmacological action of GLP-1 analogues and DPP-4 inhibitors (orange arrows/boxes) on endogenous incretin pathway (blue arrows/boxes).

compliance. Owing to their mechanism of action they can aid with weight loss.[20]

Dipeptidyl peptidase- 4 (DPP-4) inhibitors

Examples: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin.

The incretin pathway can also be modified by inhibition of the enzyme DPP-4 by the DPP-4 inhibitors. Whilst these agents can improve glycaemic control, they do not have the weight loss benefits of the GLP-1 analogues and they have been associated with pancreatitis and pancreatic cancer.[21]

Conclusion

The pharmacological management of diabetes has progressed exponentially in recent years, with multiple new formulations of insulin and new non-insulin glucose lowering agents now available. A thorough understanding of the pharmacokinetic and pharmacodynamic properties of these drugs is vital for the anaesthetist to ensure safe perioperative care of the surgical patient on glucose-lowering medication.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

References

1. National Audit Office (2015) The management of adult diabetes services in the NHS: progress review. Available from https://www.nao.org.uk/wp-content/uploads/2015/10/The-management-of-adult-diabetes-services-in-the-NHS-progress-review.pdf (accessed 28 December 2016)
2. Gale EAM, Anderson JV. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. *Kumar and Clark's Clinical Medicine*, 8th Edn. Saunders Ltd, 2012; 1001–46
3. Rang HP, Ritter JM, Flower RJ, Henderson G. The control of blood glucose and drug treatment of diabetes mellitus. In: *Rang and Dale's Pharmacology*, 8th Edn. Edinburgh: Elsevier Churchill Livingstone, 2015; 380–92
4. Barker P, Creasey PE, Dhatiraya K *et al*. "Perioperative Management of the surgical patient with Diabetes 2015" (Association of Anaesthetists of Great Britain and Ireland). *Anaesthesia* 2015; **70**: 1427–40
5. Dhatariya K, Levy N, Flanagan D *et al*., for the Joint British Diabetes Societies. Management of adults with diabetes undergoing surgery and elective procedures: Improving standards, September 2015. Available from http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Surgical_Guideline_2015_Full.pdf (accessed 28 December 2016)
6. National Patient Safety Agency. Safer Use of Insulin, Rapid Response Report, 2010. Available from http://www.nrls.npsa.nhs.uk/alerts/?entryid45=74287 (accessed 28 December 2016)
7. National Institute for Clinical and Healthcare Excellence. Type 2 diabetes in adults: management. NICE guideline NG28. 2015. Available from https://www.nice.org.uk/guidance/NG28 (accessed 28 December 2016)
8. Al-Tabakhah MM. Future prospect of insulin inhalation for diabetic patients. The case of Afrezza versus Exubera. *J Con Rel* 2015; **215**: 25–38
9. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; **50**: 1140–7
10. Inzucchi SE, Bergenstal RM, Buse JB *et al*. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140–9
11. Guardado-Mendoza R, Prioletta A, Jimenez-Ceja LM *et al*. **"**The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus**"**. *Arch Med Sci* 2013; **9**: 936–43
12. Zinman B, Wanner C, Lachin JM *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Eng J Med* 2015; **373**: 2117–28
13. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015; **38**: 1687–93
14. Eppenga WL, Lalmohamed A, Geerts AF *et al*. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care* 2014; **37**: 2218–24
15. Summary of Product Characteristics: Metformin. Available from http://www.medicines.org.uk/emc/medicine/23244/SPC (accessed 28 December 2016)
16. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Eng J Med* 2007; **356**: 2457–71
17. Consoli A, Formoso G. Do thiazolidinediones still have a role in treatment of type 2 diabetes?. *Diabetes Obes Metab* 2013; **15**: 967–77
18. Nauck M, Stockmann F, Edert R, Creutzfeldt W. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986; **29**: 46–52
19. Linnebjerg H, Park S, Kothare PA *et al*. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008; **151**: 123–9
20. Thong KY, Jose B, Sukumar N *et al*. Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. *Diabetes Obes Metab* 2011; **13**: 703–10
21. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013; **62**: 2595–604