DIABETIC MEDICATIONS AND THEIR TOXIDROMES:

INSULIN:

DELIBERATE SELF-ADMINISTERED INSULIN OVERDOSE CAUSES PROFOUND AND PROLONGED HYPOGLYCAEMIA THAT MAY RESULT IN LIFE-THREATENING SEIZURES, COMA AND PERMANENT NEUROLOGICAL INJURY

RISK ASSESSMENT:

- If deliberate → persistent hypoglycaemia and resultant neurological injury if not treated aggressively
- HYPOGLYCAEMIA MAY LAST FOR DAYS
- The severity and duration of hypoglycaemia is UNPREDICTABLE, it does not correlate well with dose and is not dependent on the insulin preparation
- Poor outcome with delayed presentation and established hypoglycaemic coma but prognosis is excellent with early effective glucose replenishment

TOXIC MECHANISM:

- Insulin stimulates transfer of glucose, potassium, phosphate and magnesium into cells
- Promotes synthesis and storage of glycogen, protein and triglycerides

TOXICOKINETICS:

- In overdose, the pharmacokinetic principles of insulin change
    - The duration of action is PROLONGED (days) and does not depend on the type of insulin used, instead it is determined by the slow and erratic release from subcutaneous adipose tissue at the injection site

CLINICAL FEATURES:

- **OBVIOUSLY, ARE THOSE OF HYPOGLYCAEMIA**
- Manifest within two hours of administration and the hyperinsulinaemic state persists for >3 days
- Autonomic → N+V, diaphoresis
- CNS → tremor, seizures, hemiplegia, coma
- Persistent and untreated hypoglycaemia → permanent neurologic injury and death

INVESTIGATIONS:

- Perform BSL every 15 minutes during resuscitation and 1-2 hours during glucose infusion
- Monitor EUC, phosphate and magnesium → replace as necessary
- Insulin levels not clinically useful unless ENDOGENOUS HYPERINSULINAEMIC STATE SUSPECTED (c-peptide as well)

MANAGEMENT:

- Administer IV glucose if BSL <4 with symptoms
    - 50mL of 50% if adult
    - 5mL/kg of 10% if child

- Commence 10% glucose infusion at 100mL/hour and give further boluses of concentrated glucose if required
    - If this fails to maintain normoglycaemia → Central access and commence titrated infusion of 25% or 50% glucose
    - Infusion rates of 150mL/hour of 50% often required for days
- Anticipate the need for large ongoing glucose requirements early and obtain early central access
    - Diabetic patients have blunted counter-regulatory response and hence need larger glucose requirements
    - Withdrawal of the infusion should be gradual → monitor for 6 hours post cessation
    - Excessively prolonged glucose infusion in NON-DIABETICS can trigger endogenous insulin secretion
    - Glucagon is ONLY A TEMPORISING MEASURE WHILE GAINING ACCESS

METFORMIN:

CAN PRODUCE LIFE-THREATENING LACTIC ACIDOSIS → IN THERAPEUTIC DOSES IN PATIENTS WHO DEVELOP RENAL FAILURE OR (LESS COMMONLY) IN THOSE FOLLOWING LARGE INGESTIONS

EARLY RECOGNITION AND HAEMODIALYSIS ARE LIFE-SAVING

RISK ASSESSMENT:

- Lactic acidosis in the setting of therapeutic metformin doses in a patient with ARF or severe sepsis carries a 50% mortality rate
- Deliberate overdose is usually benign, threshold dose unknown but thought to be ~>10g
- Lactic acidosis following acute overdose more likely if there is pre-existing renal failure or if cardiotoxic drugs are co-ingested which will impair renal perfusion
- Prognosis for lactic acidosis following deliberate overdose remains good if there is early recognition and prompt institution of haemodialysis

TOXIC MECHANISM:

- Metformin inhibits gluconeogenesis, reduces hepatic glucose output and stimulates peripheral glucose uptake
- The chief agent of toxicity IS LACTATE → type B (non-aerobic) lactic acidosis

TOXICOKINETICS:

- Elimination is ENTIRELY RENAL DEPENDENT

CLINICAL FEATURES:

- Acute overdose usually asymptomatic
- Lactic acidosis, if it develops, will manifest hours following overdose → nonspecific features → may progress to shock, coma and death
- Hypoglycaemia is usually minor and may not occur at all
- In those with lactic acidosis on therapeutic metformin have co-existing illness with near universal ARF and/or severe sepsis

MANAGEMENT:

- Resuscitate along standard lines
- Sodium bicarbonate for severe acidosis as temporizing measure
- Oral activated charcoal to those who present within 2 hours of overdose on more than 10g
- ENHANCED ELIMINATION:
    - Haemodialysis rapidly corrects acidosis and removes metformin → hence preventing further lactate formation
    - Urgently indicated if:
        - Any unwell patient with lactic acidosis from therapeutic administration
        - Worsening lactic acidosis following acute overdose where signs of instability are emerging

- Those who deliberately overdose on more than 10g should be observed for ~ 8 hours → if bicarbonate normal at the end of this period → discharge

SULFONYLUREAS:

INCLUDES GLIBENCLAMIDE, GLICLAZIDE, GLIMEPIRIDE, GLIPIZIDE

RESULTS IN PROFOUN AND PROLONGED HYPOGLYCAEMIA WITH ONSET USUALLY WITHIN 8 HOURS OF INGESTION

HYPOGLYCAEMIA CAN ALSO DEVELOP AT THERAPEUTIC DOSES, PARTICULARLY IN THE SETTING OF ACQUIERED OR PRE-EXISTING RENAL DYSFUNCTION

EARLY ADMINISTRATION OF OCTREOTIDE, GREATLY SIMPLIFIES SUBSEQUENT MANAGEMENT

RISK ASSESSMENT:

- Acute poisoning can result in profound hypoglycaemia
- Ingestion of just one tablet in non-diabetics can produce hypoglycaemia
- Hypoglycaemia is prolonged and relapse is common following initial resolution following glucose
- The hypoglycaemic response is more severe in the non-diabetic patient
- Onset may be delayed by up to 8 hours (even longer if controlled release preparations)

TOXIC MECHANISM:

- Stimulate endogenous insulin release from pancreatic beta cells through inhibition of potassium efflux

TOXICOKINETICS:

- Metabolism is hepatic to active and inactive metabolites
- Excretion is renal

CLINICAL FEATURES:

- AUTONOMIC AND CNS MANIFESTATIONS OF HYPOGLYCAEMIA

MANAGEMENT:

- Administer IV glucose as part of the initial resuscitation of the patient who is already hypoglycaemic
- Maintain euglycaemia with continued glucose infusion until octreotide can be started
- DECONTAMINATION with charcoal up to one hour for immediate release and 4 hours for controlled release preparations
- ANTIDOTES:
    - OCTREOTIDE:
        - Give 50microg IV bolus followed by 25 microg/hour continuous infusion for at least 24 hours
        - Give kids 1microg/kg bolus followed by 1microg/kg/hour infusion

        - It is an analogue of SOMATOSTATIN that is longer acting → strongly suppresses endogenous insulin release from pancreatic islet cells
- TAKE CARE NOT TO IGNORE SUGARS LESS THAN FOUR IN SULFONYLUREA OVERDOSE → HERALDS PROFOUND HYPOGLYCAEMIA
- Recurrent administration of concentrated glucose stimulates endogenous insulin release and may lead to rebound hypoglycaemia → early octreotide crucial