Chapter
1

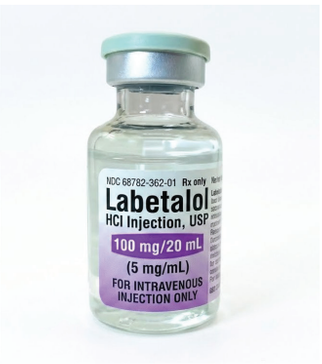
Drugs for Pre-Eclampsia, Eclampsia and Gestational Diabetes Mellitus

DRUGS FOR PRE-ECLAMPSIA (ANTIHYPERTENSIVES)
- Labetalol
- Methyldopa
- Hydralazine
- Nifedipine

DRUGS FOR ECLAMPSIA (ANTICONVULSANTS)
- Magnesium sulphate
- Diazepam
- Phenytoin

DRUGS FOR GESTATIONAL DIABETES MELLITUS
- Metformin
- Glibenclamide
- Insulin

LABETALOL



Introduction
- Alpha-1 and non-selective beta blocker

Mechanism of action

- Prevents reflex sympathetic drive and vasodilation
- Reduces peripheral vascular resistance

Preparations

- Oral and injectable

Dosage

- Oral: 100 mg BD-TDS
- Max: 2400 mg/day
- *Intravenous:* 20 mg, followed by 40 mg (after 20 mins) + 80 mg (after 20 mins) + 80 mg (after 20 mins) + 80 mg (after 20 mins)

Pharmacokinetics

- Onset
  PO: 20–120 mins and IV: 2.5 mins
- Peak effect:
  PO: 1–4 hr and IV: 15 mins
- Metabolism: Conjugation to glucuronide metabolites
- Elimination: t½(PO): 6–8 hr and t½(IV) is 5 hr

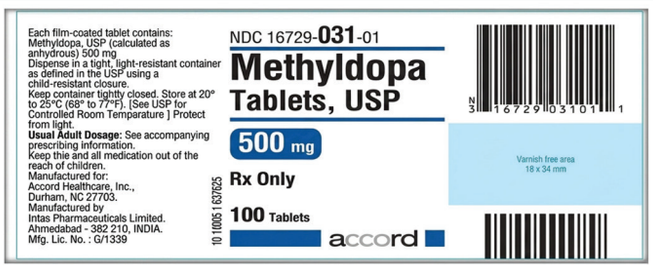
Adverse effects

- Pregnancy category: C (benefits outweigh risks)
- Very few
- Lethargy, dizziness, light-headedness
- Exercise intolerance

Contraindications

- Asthma
- Pre-existing myocardial diseases
- Heart block
- Bradycardia

ALPHA METHYLDOPA



Introduction

- Brand name: Aldomet, Dopamet
- Centrally acting antihypertensive

Mechanism of action

- Agonist of pre-synaptic alpha-2 receptors
- Inhibition of DOPA decarboxylase (preventing DOPA to dopamine to norepinephrine)
- Prevent adrenergic neurotransmission
- Sympatholytic action
- Reduces blood pressure

Dosage

- 250 mg TDS–QID

Pharmacokinetics

- Onset: 3–6 hr
- Duration: 12–24 hr
- Metabolized: Liver

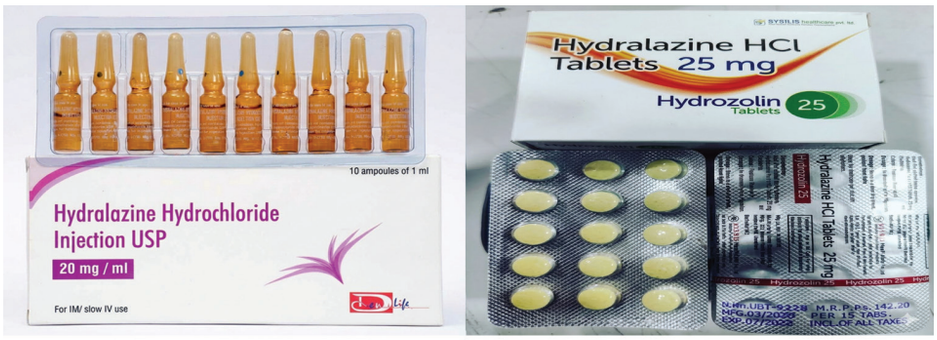
Adverse effects

- Pregnancy category: B (acceptable, no animal study shows risk)
- Fatigue
- Poor sleep
- Decreased salivation
- Elevated liver enzymes
- Positive Coombs test
- Haemolytic anaemia (rare)
- Depression (increased risk of postpartum depression)

Contraindications

- Active liver disease
- Concomitant MAO-inhibitors

HYDRALAZINE



FDA Category-C

Mechanism of action

- Relaxes arterial smooth muscle leading to peripheral vasodilation

- Interferes with calcium movement in the vascular smooth muscle
- Increases cardiac output and renal blood flow

Preparation and dose

- 20 mg/ml in 1 ml amp
- Initially 5 to 10 mg IV
- Followed by 10 mg doses at 15 to 20 mins intervals until a satisfactory response is achieved
- Generally, 2 doses are sufficient
- Maximum dose—40 mg
- Target response—Diastolic BP: 90–100 mmHg

Indications

- Hypertensive emergency in pregnancy

Contraindications

- Coronary artery disease, mitral valve disease

Side effects

Maternal

- Reflex compensatory mechanisms are evoked which cause tachycardia, increase in cardiac output and renin release → increased aldosterone → Na^+ and water retention
- Maternal hypotension
- Facial flushing, throbbing headache
- Palpitation
- Fluid retention, edema
- CHF
- Angina and MI may be precipitated
- Lupus erythematosus or rheumatoid arthritis-like symptoms

Foetal

- Late decelerations, thrombocytopenia

MAGNESIUM SULPHATE

Introduction

- It is safe and effective drug for control of seizures in eclampsia and also used prophylactically in severe pre-eclampsia

Pharmacokinetics

- The volume of distribution of magnesium is greater than that of sucrose, distribution of this ion goes beyond extracellular fluid and enters bones and cells
- Circulates—unbound to proteins
- Almost exclusively excreted in urine
- Reabsorbed in the proximal tubule by a process limited by transport maximum (T_{max})
- Its excretion increases as the filtered load increases above the T_{max}
- With normal renal function, the half-time for excretion is about 4 hours
- Half-time of excretion is prolonged in women with a decreased GFR

Mechanism of action

- Reduced presynaptic release of the neurotransmitter glutamate
- Blockade of glutamatergic N-methyl-D-aspartate (NMDA) receptors
- Potentiation of adenosine action
- Improved calcium buffering by mitochondria
- Blockage of calcium entry via voltage-gated channels

Regimes

Pritchard regime

- *Loading dose:* 4 g (20%) IV and 5 g (50%) IM in each buttock
- *Maintenance dose:* 5 g (50%) IM 4 hourly in alt buttock

Zuspan regime

- *Loading dose:* 4 g (20%) IV over 10 min
- *Maintenance dose:* 1 g/hr IV (20%) infusion

Magnesium sulfate to be continued for 24 hours after delivery or 24 hours after last seizure, whichever is later.

Others

- Dhaka/Sibai/Sholapur Regimens

Adverse effects

- Neuromuscular blockade—diminished DTR, somnolence, flaccid paralysis
- Respiratory paralysis—diaphragm and respiratory muscles paralysis
- Bradycardia
- Hypotension
- Electrocardiogram changes (P–Q interval prolongation and widened QRS complex)
- Cardiac arrest

Toxicity levels

- 4–7 mEq/L: Therapeutic range 7–10 mEq/L: ECG changes
- 10 mEq/L: Loss of DT reflexes
- 12 mEq/L: Respiratory paralysis 25 mEq/L: Cardiac arrest

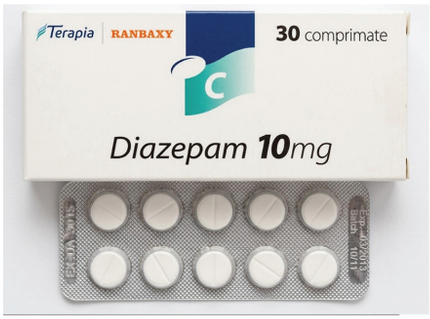
Management of toxicity

- If toxicity detected

Mild-to-moderate respiratory depression

- Stop the infusion
- Calcium gluconate or calcium chloride 1 g (10 ml of 10% injection) IV over 10 mins
- Effects of intravenously calcium may be short lived. Severe respiratory depression/arrest:
  - Tracheal intubation
  - Mechanical ventilation

DIAZEPAM



Introduction

- It is benzodiazepine derivative. It is available as tablets (10 mg) and injections (10 mg/2 ml ampules)

Mechanism of action

- It acts preferentially on midbrain ascending reticular formation and on limbic system. It acts by enhancing pre-synaptic/post-synaptic inhibition through specific benzodiazepine receptors, which is an important part of GABA receptor chloride channel complex.

Preparation

- It should not be given in plastic bags or tubing as it precipitates. It is best infused undiluted via a syringe.

Pharmacokinetics

- It is metabolized in liver by dealkylation and hydroxylation to many metabolites some of which may be active.

Adverse effects

Maternal

- Respiratory depression
- Bradycardia
- Hypotension
- Shock
- Paradoxical hyperexcitability

Foetal/Neonatal

- Decreased foetal heart rate variability
- Neonatal depression
- Hypotonia
- Neonatal hypotension
- Poor sucking reflex
- Neonatal withdrawal syndrome
- Impaired thermoregulation
- Hyperbilirubinaemia
- Oral clefts

Uses

- *Eclampsia:* Kawalhekar regimen—40 mg IV stat followed by 10 mg/hr 6 hourly for 24 hr after delivery.
- *Pre-eclampsia:* 10 mg, 8–12 hourly orally
- Status epilepticus

PHENYTOIN

Introduction

- It is used primarily in the management of seizures.

Mechanism of action

- Phenytoin produces its anticonvulsant activity through blocking sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady state inactivation.

Dosage: 10 mg/kg body weight

Adverse effects

- Severe low blood pressure and abnormal heart rhythms can be seen with rapid infusion of IV phenytoin. IV infusion should not exceed 50 mg/min in adults
- Nystagmus, double vision, sedation, slurred speech, cerebellar ataxia, and tremor

Advantages: No maternal or foetal CNS depression

METFORMIN

It is a biguanide derivative and chemical structure is related to guanidine.

Mechanism of action

- Suppress hepatic glucose production.
- Increases insulin sensitivity, enhances peripheral glucose uptake.
- Decreases insulin-induced suppression of fatty acid oxidation and decreases the absorption of glucose from the gastrointestinal tract.
- Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors.

Uses

- Type 2 diabetes
- Polycystic ovarian syndrome
- Diabetes mellitus and pregnancy
- Weight change

Side effects

Gastrointestinal upset, lactic acidosis

GLIBENCLAMIDE

Introduction

- It is an oral 2nd generation sulphonylurea (glibenclamide/glyburide) antidiabetic preparation with a hypoglycaemic effect.

Available preparation

- Available in doses of 1.25 mg, 2.5 mg and 5 mg.

Mechanism of action

- The medication works by binding to and inhibiting the ATP-sensitive potassium channels (KATP) inhibitory regulatory subunit sulfonylurea receptor 1 (SUR1) in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening voltage-dependent calcium channels. This results in an increase in intracellular calcium in the pancreatic beta cell and subsequent stimulation of insulin release.

Dosage

- Initial dosing is usually 2.5 mg daily, gradually increased by half a tablet (2.5 mg) in a stepwise manner.

Indications

- It is used to control blood glucose levels in patients with type 2 diabetes mellitus and has recently found use in gestational diabetes mellitus especially in patients with postprandial hyperglycemia.
- It is used in conjunction with diet control and exercise to control blood sugar.
- Daonil can be used alone, or in combination with insulin or other anti-diabetic drugs.

Side effects

- 10 % people show features of hypoglycemia (include weakness, trembling or shaking, sweating, light headedness, headache, dizziness, lack of concentration, tearfulness or crying, irritability, hunger and numbness around the lips and fingers) and unusual weight gain.
- 10 % people present with nausea, vomiting, heartburn, indigestion, cramps, diarrhoea, constipation or a feeling of fullness in the stomach, loss of appetite, headache, weakness, blurred or double vision.
- Less than 1% may present with blindness, jaundice, seizures, deafness, lactic acidosis and anaemia.

Contraindications

- Glibenclamide may be not recommended in those with G6PD deficiency, as it may cause acute haemolysis.
- It is generally not recommended during pregnancy but can be used during breastfeeding.

INSULIN

Introduction

- Insulin is a peptide hormone produced by β-cells of the pancreas that regulates carbohydrate, fat, and protein metabolism by facilitating cellular uptake of glucose.

Chemistry and structure

- Polypeptide hormone
- Composed of two chains (A and B) linked by disulfide bonds
- Synthesized as proinsulin, then cleaved to insulin and C-peptide

Mechanism of action

- Binds to tyrosine kinase insulin receptors
- *Increases*
  - Glucose uptake in muscle and adipose tissue
  - Glycogenesis, lipogenesis, protein synthesis
- *Decreases*
  - Gluconeogenesis, glycogenolysis, lipolysis

Types of insulin

- *Rapid-acting:* Lispro, Aspart
- *Short-acting:* Regular insulin
- *Intermediate-acting:* NPH
- *Long-acting:* Glargine, Detemir

Classification and pharmacokinetics of insulin

Type	*Insulin*	*Onset (hour)*	*Peak (hour)*	*Duration (hour)*
Rapid acting	Insulin lispro	0.2–0.4	1–2	3–5
Rapid acting	Insulin aspart	0.2–0.4	1–1.5	3–5
Short acting	Regular (soluble) insulin	0.5–1	2–4	6–8
Intermediate acting	Neutral protamine Hagedorn	1–2	8–10	20–24
Long acting	Insulin glargine	2–4	5–12	24

Doses

Insulin requirement according to gestational age	
Weeks gestation	***Total daily insulin (µ/kg/d)***
First trimester	0.7–0.8
Second trimester	0.8–1
Third trimester	0.9–1.2

In commonly used regimen for insulin administration, total insulin requirement is calculated using above table and out of the total dose calculated, 2/3 dose is given in morning (2/3 NPH and 1/3 regular insulin) and 1/3 dose in evening (1/2 as NPH and 1/2 as regular insulin).

Intrapartum Management of Gestational Diabetes Mellitus

First Stage Labour Management

Insulin management during labour

- Usual dose of intermediate-acting insulin is given at bedtime.
- Morning dose of insulin is withheld.
- Intravenous infusion of normal saline is begun.
- Once active labor begins or glucose levels decrease to less than 70 mg/dl, infusion is changed from saline to 5% dextrose and delivered at a rate of 100–150 cc/h (2.5 mg/kg/min) to achieve a glucose level of approximately 100 mg/dl.

- Glucose levels are checked hourly using a bedside meter, allowing for adjustment in the insulin or glucose infusion rate.
- Regular short-acting insulin is administered by intravenous infusion at a rate of 1.25 U/h, if glucose levels exceed 100 mg/dl.

Other way of maintaining euglycemia

Make an infusion in an infusion syringe by adding 4 U of regular insulin in 50 ml NS and then give at the following rates as per requirement:

Blood glucose (mg/dl)	*Insulin requirement*	*Infusion rate*
120–140 mg/dl	0.8 U/hr	10 ml/hr
140–180 mg/dl	1.2 U/hr	15 ml/hr
>180 mg/dl	1.6 U/hr	20 ml/hr
<70 mg/dl	Give 5% D	10 ml/hr

Adverse drug reaction

- Hypoglycaemia is the most commonly observed and serious problem associated with insulin therapy. The body's response to hypoglycaemia occurs through two mechanisms: Sympathetic stimulation and the neuroglucopenic effect. These responses may be less pronounced in conditions such as long-standing diabetes or with the concomitant use of drugs, such as beta-blockers.
- Insulin promotes the movement of potassium into the cells, resulting in hypokalemia, which, if not treated promptly, may lead to respiratory paralysis, ventricular arrhythmia, and death.
- *Local reaction:* Redness, pain, swelling in injection site.