5

Intravenous Induction Agents

These anaesthetic drugs are used via intravenous (IV) route to produce induction during general anaesthesia. "Induction" means unconsciousness and no response to external stimuli. Usually, eyelash reflex absence is taken as induction. This implies that neural activity in the patient's brain has decreased to a level that there is no response to the stimuli. Obviously, depending on the strength of stimuli, there can be a response, e.g. during laryngoscopy, which is a very strong stimulus. This usually causes sympathetic activation leading to increase in heart rate, blood pressure, especially in adult patients.

Main intravenous induction used in clinical practice are:

- Propofol
- Thiopentone sodium
- Ketamine
- Etomidate
- Midazolam.

Propofol is the most commonly used intravenous (IV) induction agent. It provides a rapid, smooth recovery. Main side effects of propofol are related to cardiovascular system (hypotension).

Thiopentone was most commonly used IV induction agent before propofol came into clinical practice. Longer

duration for complete awakening and inability to use it in infusion form are the major differences from propofol.

Ketamine has strong analgesic properties unlike other induction agents. However, its clinical effects (tachycardia, increased BP, increase in secretion, emergence reactions) limit the usefulness.

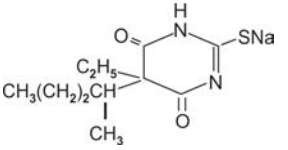
Etomidate property of adrenocortical suppression has limited the role of this drug (no infusion or multiple doses).

Midazolam is a benzodiazepine. This drug is used as an anxiolytic and sedative. Use in high dosage can lead to induction of anaesthesia. Midazolam has been used for pre-operative sedation by the intravenous, intramuscular, rectal, oral, and nasal routes.

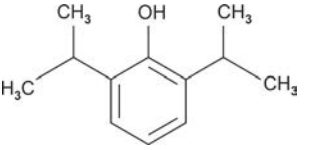
PREPARATION

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Available as white emulsion containing soyabean (10%), glycerol (2.25%), purified egg phosphatide (1.2%), disodium edentate (0.005%). • 1% or 2% propofol solutions are used.	• Available as sodium salt mixed with 6% anhydrous sodium carbonate (500 mg or 1 g vials used). This maintains alkalinity of thiopentone solution in presence of atmospheric carbon dioxide. • High alkaline nature prevents microbial growth so solutions are stable for 1 week if refrigerated. In powder form, the drug is stable indefinitely at room temperature. • Thiopentone powder is reconstituted in water or saline with pH around 10.5 (alkaline as it is more than 7.4). Only 2.5% solution is given intravenously. 5% or 10% solution can be given rectally.	• 10 mL vial and 1 mL ampoules containing 50 mg/mL of ketamine hydrochloride are available. • Benzethonium chloride 0.01% w/v is the preservative used in vials while ampoules are preservative-free.	• Propylene glycol is the preservative used with etomidate. Its commercial preparation contains 2 mg/mL of etomidate and 35% propylene glycol with water. Lipid emulsion is available. • Propylene glycol causes mild haemolysis. • On prolonged infusion, it causes problem with plasma osmolality (solution osmolality = 4640 mOsm/L)

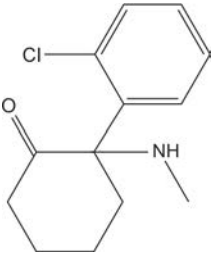
STRUCTURE ACTIVITY RELATIONSHIP[1] (FIG. 5.1)



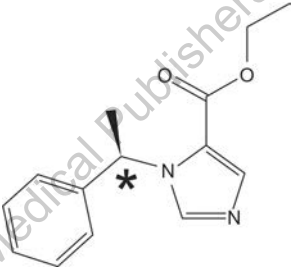
Thiopentone sodium
(sulphur atom at second carbon atom)



Propofol



Ketamine



Etomidate (chiral centre as asterisk)

Fig. 5.1 Chemical structure of thiopentone, propofol, ketamine and etomidate

CHEMICAL STRUCTURE

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• It is an alkyl phenol derivative. • Chemically, it is 2, 6, di-isopropyl phenol. • As we know, phenols are oils at room temperature, propofol is, therefore, insoluble in aqueous solution but highly lipid soluble.	• Barbiturates are derived from barbituric acid which itself is formed from urea and malonic acid Urea + malonic acid ↓ Barbituric acid ↓ Barbiturates Oxy ↓ thio Oxybarbiturate has oxygen at C2 while thiobarbiturate has sulphur at C2 • Addition of sulphur at C2 position (thio--) causes increase in lipid solubility, rapid onset after injection and short duration of action as compared to oxybarbiturates. • Length of side chain at C5 position determines the potency and duration of action. • Longer and branched chains give high potency and increased duration of hypnosis to the compound. • Addition of methyl group at C1 results into a drug (such as methohexital) with rapid onset, short duration of action along with increased incidence of excitatory phenomenon, e.g. Myoclonus.	• It is a phencyclidine derivative • It exists as S + and R – optical isomers • S+ isomer is 3–4 times more potent than R– form. S(+) *ketamine* produces more intense analgesia, has more rapid metabolism, less salivation, and a lower incidence of *emergence reactions* than R(–) *ketamine.*	• It is a carboxylatedimidazole derivative. • Imidazole nucleus is like midazolam, which makes this drug water soluble at acidic pH and lipid soluble at pH 7.4 (physiological pH). • Chemical name is R-1-(1ethylphenyl) imidazole-5-ethyl ester[2]

MECHANISM OF ACTION

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Mechanism of action is mediated via GABA as well as NMDA subtype of glutamate receptor. • Increase in GABA induced chloride current.[3] • Inhibition of NMDA subtype of glutamate receptor.[4]	GABA facilitatory action-barbiturates bind to GABA receptors and prolong the duration of binding of GABA with its receptor. This leads to prolonged opening of Cl^- channel. GABA mimetic action—At high concentration barbiturates directly cause opening of Cl^- channel and cell membrane hyperpolarisation (barbiturate anaesthesia)	Depresses some parts of thalamus and neo-cortex while stimulates limbic system. This leads to what is called as dissociative anaesthesia. EEG demonstrates a dominant theta activity with abolition of alpha rhythm. It interacts with NMDA and probably opioid receptors. Patient is not in normal sleep but in a cataleptic state.	• Probably GABA-mediated • $GABA_a$ receptors are activated. There seems to be no major effect on ion channels[5]

Abbreviations: GABA, Gamma aminobutyric acid; NMDA, N-methyl-D-aspartate

PHARMACOKINETICS

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Highly lipid-soluble drug which is distributed rapidly to the vessel-rich group. • Action terminates due to redistribution. • Metabolised in liver to inactive glucuronide and sulphate conjugates and corresponding quinol. • Extrahepatic metabolism also present.[6] • Liver and renal impairment do not affect the metabolism significantly. • Metabolites are inactive and its rapid clearance from the plasma allows the drug to be administered as continuous infusion without excessive cumulative effect.[7] • Initial distribution half- life is 2–8 minutes.	IV administration of thiopental ↓ Distribution to vessel-rich group (e.g. brain) ↓ Induction of anaesthesia ↓ Redistribution to less well perfused tissue (muscle) ↓ Termination of induction (Awakening) ↓ Redistribution to poorly perfused tissue (fat) ↓ Elimination by metabolism in liver (oxidation, desulfuration) ↓ Metabolites excreted via kidneys. Plasma drug levels increase when repeat or large doses are given due to deposition in fat, slow elimination	• It is highly lipid soluble drug with distribution pattern similar to thiopentone • Oral bioavailability is around 20%, via intra-nasal route is 40%[8,9] • Metabolised in liver to hydroxy-norketamine (metabolite II) and norketamine (metabolite I). Norketamine is 20–30% active as compared to parent compound. Metabolites excreted in urine. • Alteration in hepatic blood flow effect clearance, e.g. halothane decreases clearance • Causes acceleration of its own metabolism by enzyme induction. This is probably the mechanism behind tolerance to its analgesic effect after repeated doses (e.g. in burn patients when repeated doses used for dressing)	• Awakening after single bolus dose of etomidate is more rapid than thiopentone • Prompt awakening after an induction dose is due to redistribution • Rapid meta-bolism may also contribute • Metabolised in liver via hydrolysis into inactive metabolites which are excreted in urine

The metabolism of thiopentone is normally a first-order process; however, once plasma concentrations become high, metabolism becomes a zero-order process (i.e. rate of elimination becomes constant rather than dependent upon plasma concentration). This happens due to limited availability of enzyme. Also, thiopentone is metabolised to pentobarbital, which is also a sedative and excreted slowly. So, thiopentone is not used for infusion unless absolutely indicated.

CENTRAL NERVOUS SYSTEM EFFECTS

Neurotransmitters in human brain can be classified broadly into two groups:

1. Small molecule (rapidly acting transmitters):
   e.g. norepinephrine, glycine, dopamine, acetylcholine, GABA, serotonin.
2. Neuropeptides:
   e.g. substance P, enkephalin, thyrotropin-releasing hormone, ACTH.

Small molecule (rapidly acting transmitters) are involved in acute responses of the nervous system. They are either inhibitory or excitatory.

- Acetylcholine
  - Mainly excitatory
  - Some actions inhibitory
- Glutamate
  - Excitatory
- Norepinephrine
  - Mainly excitatory
  - Some inhibitory effects
- GABA
  - Inhibitory
- Dopamine
  - Usually inhibitory
- Glycine
  - Inhibitory

- Serotonin
  - Inhibitor of pain pathways.

Anaesthetic agents act via potentiation or activation of these inhibitory or excitatory pathways.

Gaba (ϒ-Aminobutyric Acid)

GABA is the principal inhibitory neurotransmitter in human brain. GABA receptors are of two types: $GABA_A$ and $GABA_B$. Out of these, $GABA_A$ receptors are made up of 5 sub-units namely α, β, γ, δ and ρ. These sub-units are proteins. They form a complex to produce a chloride ion channel when they are inserted into cell membrane.

Activation of $GABA_A$ receptor leads to increased chloride conductance (Cl^-) and thus hyperpolarise the cell membrane. This reduces the excitability of neurons. Many anaesthetic agents act via re-$GABA_A$ receptors. There are specific binding sites present on these receptors for various drugs, e.g. barbiturates, benzodiazepines, propofol, etc.

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Unconsciousness occurs with induction doses while subhypnotic doses produce amnesia and sedation. Does not possess analgesic properties. • Produces decrease in cerebral blood flow and oxygen requirement.[11]	• Produces unconsciousness with induction doses. Subhypnotic doses may cause increase in sensitivity to pain (hyperalgesia). It causes progressive suppression of cortical activity and can finally lead to flat EEG at high doses. • Produces dose-dependent decrease in cerebral metabolism, cerebral blood flow and cerebral oxygen requirement.[15]	• Produces a dissociative state along with amnesia and analgesia. A cataleptic state with eyes open, nystagmus, salivation, lacrimation (increased secretions) and maintenance of airway reflexes which are non-protective, is seen. Possesses analgesic properties even at subanaeshetic doses.[10] • Causes increase in CBF, ICP and $CMRO_2$.	• Produces unconsciousness with reduction in CMR, CBF, $CMRO_2$ and ICP. No analgesic activity. • May activate seizure foci in patients with epilepsy. This feature is used for mapping of foci in neurosurgery before ablation.

Contd...

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Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• In patients with raised ICP, decrease in ICP is associated with decrease in CPP, therefore, propofol may not be beneficial. • Decreases IOP more than thiopentone. • Occasional involuntary movements can occur following induction. • Proconvulsant properties are controversial. It has been successfully used in control of refractory seizures. • Its greatest advantage over other agents is rapid and complete awakening after termination of effect. • Possesses antiemetic action.[12-14]	• Reduction in ICP is more than MAP. Thus CPP (cerebral perfusion pressure) is well maintained [CPP = MAP – ICP] IOP (intraocular pressure) is reduced. • Produces retrograde amnesia. • Seizures refractory to other anticonvulsants respond to barbiturates. • Cerebroprotective action against regional cerebral ischaemia but not global ischaemia. So, this drug will not provide much benefit during cardiorespiratory arrest-induced hypoxia. • It has greater sensitivity for cerebral cortex and reticular activating system.	• Causes increase in IOP. Contraindicated in patients with glaucoma. • Undesirable emergence reactions are seen with ketamine. They occur at the time of awakening and manifest as unpleasant dreams, aggressiveness, violence, sense of floating. These reactions are associated with misinterpretation of visual and auditory stimuli. • They occur mostly in 1st hour of awakening and more common with large dose, in females, in old age. Management includes benzodiazepines (00.5–0.1 mg/kg midazolam IV) or droperidol given before or with the administration of ketamine. • Though return of consciousness after ketamine anaesthesia may occur in 10–15 minutes but complete recovery is often delayed.[16-18]	• Myoclonus is common during etomidate induction. • EEG changes produced are same as barbiturates.[19]

Abbreviations: ICP, intracranial pressure; CPP, cerebral perfusion pressure; EEG, electroencephalogram; CBF, cerebral blood flow; IOP, intraocular pressure; $CMRO_2$, cerebral metabolism of oxygen

CARDIOVASCULAR SYSTEM EFFECTS

Cardiovascular effects of intravenous agents are studied with reference to:

- *Effect on preload (venodilation)*: Preload is defined as stretching of ventricular fibres just before contraction. Determined by end diastolic volume or pressure.
- *Effect on afterload (systemic vascular resistance)*: Afterload is defined as resistance against which ventricle has to eject blood. Determined by systolic pressure.
- Effect on heart rate
- Effect on cardiac contractility
- Effect on central sympathetic outflow
- Effect on myocardial oxygen demand–supply ratio.

As a general rule, volume depleted patients are more likely to show profound hypotension. Concomitant use of other drugs and their effect on cardiovascular system should always be kept in mind while anticipating haemodynamic effects in a particular patient (e.g. opioids + benzodiazepine) cause marked CVS depression; while single use of each group does not produce major haemodynamic changes.

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Dose and blood concentration-dependent fall in blood pressure usually to a greater extent than comparable dose of thiopentone. MAP, systolic and diastolic pressures fall from preinduction values. *Mechanism* – Venodilation and peripheral pooling (decrease pre-load) – Fall in systemic vascular resistance – Decreased cardiac contractility – Reflex tachycardia does not occur due to attenuation of baroreceptor reflex mechanism. Minimal change in heart rate • Cardiac output falls due to unchanged heart rate.[20] • Fall in blood pressure is more marked in hypertensives, elderly, hypovolemics and when drug is injected rapidly. • Ketamine (0.5 mg/kg) can be given with or before propofol (ketofol) to prevent hypotension.[21] • Myocardial oxygen demand–supply ratio is well preserved if dangerous fall in blood pressure is avoided.	• In induction doses it causes transient fall in blood pressure. *Mechanism* – Venodilation and peripheral pooling of blood – Decreased cardiac contractility (minor mechanism) – Decreased central sympathetic outflow • Heart rate is increased via baroreceptor activation, vagolytic action.[22] • Cardiac output falls in spite of compensatory tachycardia, fall in BP is more marked in hypertensives because they are chronically volume depleted. • Should be cautiously used in patients who are dependent on pre-load for maintenance of cardiac output, e.g. compensated shock, pericardial tamponade. *Note:* It decreases myocardial contractility more than propofol, ketamine, etomidate and midazolam. • No tendency to cause arrhythmias.	• It causes increase in heart rate, blood pressure and cardiac output via stimulation of sympathetic system. • There is resultant increase in circulating norepinephrine. • Cardiovascular effects are not dose dependent. • Ketamine itself is a direct myocardial depressant. Under normal conditions Indirect action-(sympathetic stimulation) predominates and the patient shows increase in blood pressure and heart rate. If, however, central sympathetic outflow is blunted due to other factors (use of opioids) or body catecholamine levels are exhausted, fall in BP and cardiac output occurs. • Myocardial oxygen demand is increased. So, not preferred in ischaemic heart diseases.	• Most cardiostable intravenous inducing agent. • Heart rate, blood pressure, cardiac output and cardiac contractility show minimal change.[26] • No effect on sympathetic system. • Myocardial oxygen demand-supply ratio is well preserved.

RESPIRATORY SYSTEM EFFECTS

Respiratory effects of intravenous agents are studied under following heads:

a. Effect on respiration (rate, tidal volume)
b. Effect on responsiveness to hypercarbia and hypoxaemia
c. Effect on laryngeal and pharyngeal reflexes
d. Bronchodilation.

Most of the intravenous inducing agents (except ketamine) are centrally acting respiratory depressants. Apnoea follows large undiluted boluses. Airway assessment should always be done before giving any of these drugs. Simultaneously administered opioids accentuate respiratory depression.

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• It is a potent respiratory depressant. Apnoea might be prolonged for more than 30 seconds. • Incidence and duration of apnoea is greater than thiopentone. • Responses to hypercarbia and hypoxaemia are depressed. • Factors affecting respiratory depression (same as thiopentone). • Depression of laryngeal and pharyngeal reflexes is better than thiopentone. This facilitates insertion of LMA. • Causes bronchodilation but not as potent as halothane. Mechanism is via direct smooth muscle relaxation.	• It causes marked depression of respiration. • Both rate and depth of respiration are affected. • Apnoea can occur. • Response to hypercarbia and hypoxaemia are depressed. • Factors affecting respiratory depression: – Rate of injection – Dose and concentration of the drug – Co-administered drugs • Laryngeal reflexes are not depressed and laryngospasm can occur under light thiopentone anaesthesia. • Mucociliary action of respiratory mucosa is depressed (similar to volatile agents). • Does not cause bronchodilation.	• Respiration is rarely depressed after usual doses of ketamine but occasionally it may occur if the drug is given very rapidly or along with other CNS depressants. • Response to hypercarbia is not altered. • Drug may act as respiratory depressant in children, especially in large boluses. • Although coughing, gag reflex, swallowing are relatively intact after ketamine but they are not completely protective and silent aspiration can occur. • Bronchodilation due to direct smooth muscle relaxant effect as well as sympathomimetic action. • Bronchodilation is as potent as halothane. • Increased salivation can produce upper airway obstruction.	• Action on ventilation is minimal. Decrease in tidal volume is made up by an increase in respiratory rate. • Apnoea rarely occurs after induction doses. • Hiccups or coughing may occur during etomidate induction. • No histamine release.

Abbreviations: LMA, laryngeal mask airway; CNS, central nervous system

SIDE EFFECTS

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Pain at injection site decreased by using a large vein (antecubital vein) and adding lidocaine (0.5 mg/kg) or even small dose of opioid given before.[23] • Mild involuntary muscular movements (myoclonus) during induction. • Greater incidence and duration of apnoea as compared to thiopentone. • Propofol emulsion supports bacterial growth. • The drug should be prepared under sterile conditions. Disodium edentate containing propofol retards bacteria growth. Unused propofol should be discarded after 6 hours to prevent bacterial contamination. Use venous access systems without dead space to minimize drug accumulation and bacterial growth.[24] • Fall in BP is more than thiopentone. • Rapidly crosses placenta. Effect on foetus is not greater than thiopentone.[25] • Propofol is a lipid emulsion and its infusion should be cautiously used in patients with disorders of lipid metabolism (pancreatitis). • Rarely causes thrombophlebitis.	• Garlic taste in mouth • If inadequate induction dose is used, coughing and hiccups can occur. • Mechanism is depression of inhibitory areas in brain first. No specific treatment of hiccups is recommended at present.[26] • The drug crosses placenta and is also secreted into milk. • Allergic reactions in the form of anaphylactic and anaphylactoid reactions occur rarely. • Overdose can result into severe cardiorespiratory depression. • Laryngospasm can occur if patient's airway is handled under thiopentone alone or when plane of anaesthesia is inadequate. • Thrombophlebitis can occur due to chemical irritation, especially with 5% thiopentone.	• Sympathetic system activation. Increased heart rate, BP, cardiac output, myocardial oxygen demand. • Stimulates oral secretions. • Administration of an antisialogogue (e.g. glycopyrrolate) is helpful. • Increased ICP • Increases intraocular pressure. • Nystagmus, diplopia blepharospasm can occur. • Common signs of anaesthetic depth are less reliable when ketamine is used. • Increased muscle tone. • Potentiation of neuromuscular blockers side effects intensity has no direct relation with the dose.[27]	• Nausea and vomiting. • Myoclonus during Induction. Use of dexmed (0.1 µm/kg), magsulf, thiopentone reduces myoclonus.[28,29] • Pain at injection site. • Corticosteroid and mineralocorticoid synthesis suppression. • After single induction dose, adrenal dysfunction is minimal and resolves within 12 hours.[30] • Thrombophlebitis.

CONTRAINDICATIONS

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Hypovolemia—Even after correction of hypovolemia, there may be precipitous fall in blood pressure. • Should be avoided in epilepsy, pancreatitis.	• Porphyria—Barbiturates induce the enzyme aminolevulinic acid synthetase (ALA synthetase). It causes increase in levels of porphyrin and can precipitate an acute attack. • Severe cardiovascular dysfunction. • Reduced preload leading to hypovolemia, e.g. haemorrhage, vasodilation in sepsis. • Airway diseases (risk of bronchoconstriction), impending coma (hepatic failure, renal failure, diabetes) adrenocortical failure, myxoedema severe anaemia.	• Raised ICP • Raised IOP and penetrating eye injuries. • Psychiatric disorders. • As sole anaesthetic agent in hypertensives, IHD and CVA patients.	• Epilepsy • Adrenocortical insufficiency

Abbreviations: ALA, aminolevulinic acid; ICP, intracranial pressure; IOP, intraocular pressure; IHD, ischaemic heart disease; CVA, cerebrovascular accident

Intra-arterial Injection of Drugs

Intra-arterial (IA) injection of drugs not dissolved in water (such as diazepam, propofol, and etomidate) or with an alkaline pH (like thiopental, phenytoin) should be avoided at all cost. With unintentional intra-arterial injection, both acute and chronic manifestations can be expected.

Immediate discomfort can be from local irritation to intense pain distal to the site of injection. Soon thereafter, other sensations like tingling, burning, and paraesthesias may also be complained of.

Indicators suggestive of intra-arterial cannulation include wave-like movement of blood in the IV tubing (with each heart beat), backflow of blood into the IV tubing. This is due to high arterial pressure.

Anatomical locations where arteries and veins are close (such as in the antecubital fossa, ventral wrist) should be avoided, especially in obese patient/hypovolaemic

patient. If IA placement is suspected, confirmatory testing should be performed with either arterial blood gas (ABG) or use of a pressure transducer to see the intravascular pressure.[31,32]

Pain on thiopentone injection, if stated by patient after 1–2 mL of injection, would suggest an extravascular or intra-arterial injection.

Signs and Symptoms

- Intense burning pain
- Blanching of skin
- Severe vasoconstriction and disappearance of radial pulse (if injection in forearm).

Severity of all these complications depend on the concentration, dose, total volume and the rate of injection of *thiopentone* in the artery. So, it is advisable not to use a concentration of more than 2.5%. Also, the rate of injection should be slow to appreciate any resistance to injection.

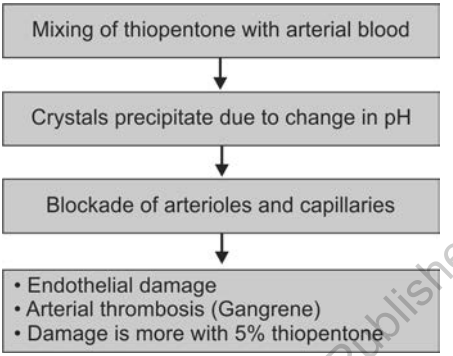
Treatment: Leave IV cannula in artery.

- Dilute the drug by injecting saline via cannula.
- Relieve vascular spasm by:
  - Inj papaverine 40–80 mg dissolved in 10–20 mL NaCl 0.9%
  - 5–10 mL of 1% xylocaine injection
  - Brachial plexus/stellate ganglion block (sympathectomy).

Propofol Infusion Syndrome

It is a life-threatening complication of prolonged high-dose propofol use, especially in the intensive care units (ICUs). Metabolic acidosis, lipemia, rhabdomyolysis, occurs in critically ill patients when propofol infusion is used. These features have no correlation with the primary disease. During prolonged infusion of propofol in ICUs, serum triglyceride levels should be monitored. Pre-disposing factors include young age, severe critical illness of central nervous system or respiratory

Flow chart 5.1 Pathophysiology of vascular thrombosis due to thiopentone injection



origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake and sub-clinical mitochondrial disease. Treatment options are limited. Haemodialysis or haemoperfusion with cardiorespiratory support has been the most successful treatment.[33,34]

Porphyrias

The *porphyrias* are disorders that arise from various inherited enzyme defects in the haem biosynthesis pathway. This leads to accumulation of porphyrins which are excreted in urine/faeces (giving them purple color). Major clinical features of porphyrias are neurological or dermatological. Classification of porphyrias can be on the basis of site (liver/RBC), type of enzyme defect, acute or non-acute.

For an anaesthetist, acute porphyrias are important to know as anaesthetic drugs and other conditions (dehydration, infection) can stimulate haem production.

Clinical features of acute porphyria are—neurological (altered mentation, muscle weakness, sensory loss, seizures), severe abdominal pain, hypertension, tachycardia.

Management is symptomatic and volume correction, pain relief should be done. There is no problem with regional anaesthesia in patients having porphyria.

Barbiturates, etomidate are the induction agents which have been implicated in precipitating an acute porphyria attack.

CLINICAL USES

Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
• Induction of anaesthesia • Maintenance of general anaesthesia • Sedation during regional anaesthesia • Sedation in ICU/for diagnostic procedures, e.g. MRI studies[35,36]	• Induction of anaesthesia • Treatment of increased ICP, especially in patients who do not respond to hyperventilation and drug-induced diuresis	Induction of anaesthesia in • Hypovolemic patients • Bronchospastic and reactive airway disease • IM induction in children with difficult IV access Maintenance of general anaesthesia	• Induction of anaesthesia in patients with cardiovascular unstability. However, its use is limited due to adrenocortical suppression even with a single dose • Post-operative nausea/vomiting is another limiting factor • Maintenance of anaesthesia
In subhypnotic doses • Used for treatment of chemotherapy-induced vomiting • Refractory postoperative nausea vomiting • Treatment of pruritis associated with neuraxial opioids	• Cerebral protection. • It can improve survival following focal brain ischeamia[37] • Refractory seizures (infusion at 3–5 mg/kg/ hr)	• For analgesia and sedation during burn dressing changes, debridement procedures, paediatric regional anaesthesia • Often a first-line drug for short, painful procedures. Excellent complementary drug (for sedation, analgesia with maintenance of respiration) if spontaneous ventilation with unobstructed airway can be maintained • Supplementation of regional anaesthesia (IV ketamine)[38-40]	

Ketamine and propofol (ketofol) combination provides analgesic sedation. There is a theoretical advantage of haemodynamic stability also. This combination can be used during insertion of LMA, burn dressings, fracture reductions in emergency (painful procedures which require a deeply sedated patient). The drugs can be combined in a 1:1 ratio and given by intermittent boluses (0.5–1 mg/kg IV).[41]

DOSES

	Propofol	*Thiopentone*	*Ketamine*	*Etomidate*
Induction dose	2–2.5 mg/kg IV reduced with increasing age	2.5–4.5 mg/kg IV in adults 5–6 mg/kg IV in children 7–8 mg/kg IV in infants	0.5–2 mg/kg IV 4–6 mg/kg IM	0.2–0.6 mg/kg IV (0.3 mg/kg is commonly used range)
Maintenance dose	50–150 µg/kg/min/IV with N_2O or an opioid	Not used due to cumulative effect	10–30 µg kg/min/IV with N_2O and oxygen.	10 µg/kg/min with N_2O and an opiate
Sedation dose	For sedation, reduce above rate by half	Not used due to anti-analgesic, accumulation properties	0.2–0.8 mg/kg IV or 2–4 mg/kg IM This is also the analgesic dose for ketamine	5–8 µg/kg/min. The drug should be used only for short periods because of inhibition of corticosteroid synthesis

BENZODIAZEPINES

Benzodiazepines are a group of drugs which produce anxiolysis, sedation, unconsciousness (depending on dose), amnesia. In addition, these drugs also have anticonvulsant and muscle relaxing property (central action).

The three drugs most commonly used are midazolam, diazepam, lorazepam.

	Midazolam	*Diazepam*	*Lorazepam*
CNS effects	Site of action is $GABA_A$ receptor in CNS. Decrease CBF, $CMRO_2$ flat EEG is not achieved unlike barbiturates. Anterograde amnesia	-Same-	-Same-
RS effects	• Dose-related respiratory depression due to central action • Rapid drug injection produces more depression	-Same-	-Same-
CVS effects	• At high doses, fall in BP d/t fall in SVR. Heart rate, cardiac output are preserved • In hypovolemic patients/ coadministration of opioid, above changes are pronounced	-Same-	-Same-
Metabolism	Liver ↓ Oxidation, conjugation ↓ Hydroxymidazolam (active metabolite). Clearance – 5–10 mL/kg/min Metabolism slows down if cytrochrome p-450 inhibiting drugs are used pH-dependent solubility due to imidazole ring (it opens at pH <4 so drug is water soluble). At pH >4, ring closes to make drug more lipid soluble. So, midazolam is lipophilic at pH = 7.4	Liver ↓ Oxidation, glucuronide conjugation ↓ Oxazepam, desmethyldiazepam (active, accumulates in renal failure) Clearance-0.2–0.5 mL/kg/min Excreted in urine	Liver • Same route but the metabolites are inactive Clearance-1–2 mL/kg/min • Metabolism minimally affected by enzyme-inducing drugs, age. Can be used in renal dysfunction without dose change

Contd...

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	Midazolam	*Diazepam*	*Lorazepam*
Uses	• Pre-operative medication to reduce anxiety • Sedation during regional anaesthesia, post-operative period, in ICUs. Dose depends on level of sedation[42] • Induction (as co-induction with propofol/opioid). Used as sole agent causes delayed induction, delayed awakening, no analgesia so, BZDs not used as sole induction agents	Oral sedation especially in adult patients	• Same as midazolam- • Not preferred as an intra-operative sedative due to slow onset, longer recovery from amnesic action • Used for status epilepticus treatment
Side effects	Short acting Respiratory depression, undesirable sedation/ prolonged amnesia in post-operative period	Long acting • Same as midazolam Also venous irritation on IV use	Intermediate acting • Same as diazepam
Doses: Sedation/ Induction	0.5 mg/kg (oral), 0.5–1 mg IV bolus till desired sedation level achieved 0.1–0.2 mg/kg	5–10 mg (oral in adults), 2–4 mg IV bolus till desired sedation 0.3–0.5 mg/kg (not preferred now)	0.2 mg IV bolus 0.1 mg/kg

All three drugs have similar protein binding (95%) and volume of distribution (1.0–1.5 L/kg).

Benzodiazepines (BZDs) do not provide analgesia, stress response to intubation is also not blunted. When used along opioids, there can be a fall in blood pressure and increased chances of respiratory depression.

Midazolam can be used via oral, intra-nasal, intra-muscular, intravenous route. Midazolam has shorter context sensitive half time, greater clearance than diazepam/lorazepam. It has an anti-emetic action also.[43]

Because of its slow onset and length of action, lorazepam is not useful in instances in which rapid awakening is necessary, such as with outpatient anaesthesia. It can be used to minimise emergence reactions due to ketamine use.

Diazepam clearance is prolonged in geriatric patients. Elimination half-life increases with increase in age.

FLUMAZENIL

This drug acts as competitive antagonist at BZD receptor. In the absence of agonist (BZD), flumazenil has little clinical effect on respiratory or cardiovascular system.

The drug is metabolised in liver and metabolites are excreted in urine.

Doses – 0.2 mg bolus, up to 3 mg to reverse BZD actions (sedation, respiratory depression). It has a rapid onset with peak effect within 5 minutes and the duration of action lasts up to 30 minutes. Reversal of amnesic effect is less than respiratory depression effect.

To prevent resedation, infusion (0.5–1 μg/kg/min) can be started as this drug has a short half-life.

Factors affecting intravenous induction drug dosage:

Age—dose of thiopentone, propofol is increased in paediatric age group due to higher central volume and higher clearance.

In old age, dose decreases due to low clearance and reduced central volume.

Pre-operative American Society of Anesthesiologists (ASA) status—drug requirements are reduced in ASA 3/4/E patients. Use your clinical judgement and give titrated doses.

Pre-medication—heavy pre-medication will reduce the dose of induction agents in most of the cases.

So, dose given above should be used according to clinical status of patients.

The end-point of induction is always the same irrespective of the agent used. There should be minimal

haemodynamic change during any noxious stimulus (clinical observation).[44]

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