## GENERAL ANAESTHETICS AGENTS

**Def:-** General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

→ Loss of all sensation, especially pain.

→ Sleep (unconsciousness) and amnesia.

→ Immobility and muscle relaxation.

→ Abolition of somatic and autonomic reflexes.

### MECHANISM OF ACTION OF ANAESTHETIC DRUGS :-

Unlike most drugs, inhalation anaesthetics, which include substances as diverse as **halothane**, **nitrous oxide** and xenon, belong to no recognizable chemical class. The shape and electronic configuration of the molecule is relatively un important, and the pharmacological action seems to require only that the molecule has certain physicochemical properties.

### *LIPID THEORY:-*

→ Overton and Meyer, showed a close correlation between anaesthetic potency and lipid solubility in a diverse group of simple and unreactive organic compounds. This led to a bold theory, formulated by Meyer in 1937: 'Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipids of the cell'.

→ The relationship between anaesthetic activity and lipid solubility has been repeatedly confirmed. Anaesthetic potency in humans is usually expressed as the *minimal alveolar concentration (MAC)* required to abolish the response to surgical incision in 50% of subjects. Figure 1 shows the correlation between MAC (inversely proportional to potency) and lipid solubility, expressed as oil:water partition coefficient, for a wide range of inhalation anaesthetics. The Overton-Meyer studies did not suggest any particular mechanism, but Oil:water partition was assumed to predict partition into membrane lipids, consistent with the suggestion that anaesthesia results from an alteration of membrane function. Introduction of inert foreign molecules into the lipid bilayer could cause a functional disturbance is not explained by the lipid theory. Two possible mechanisms, namely *volume expansion* and *increased membrane fluidity*, have been

suggested and tested experimentally, but both are now largely discredited, and attention has swung from lipids to proteins, the correlation of potency with lipid solubility being explained by the effect of lipid solubility on the concentration of anaesthetic adjacent to its supposed protein target in the hydrophobic region of neuronal cell membranes.

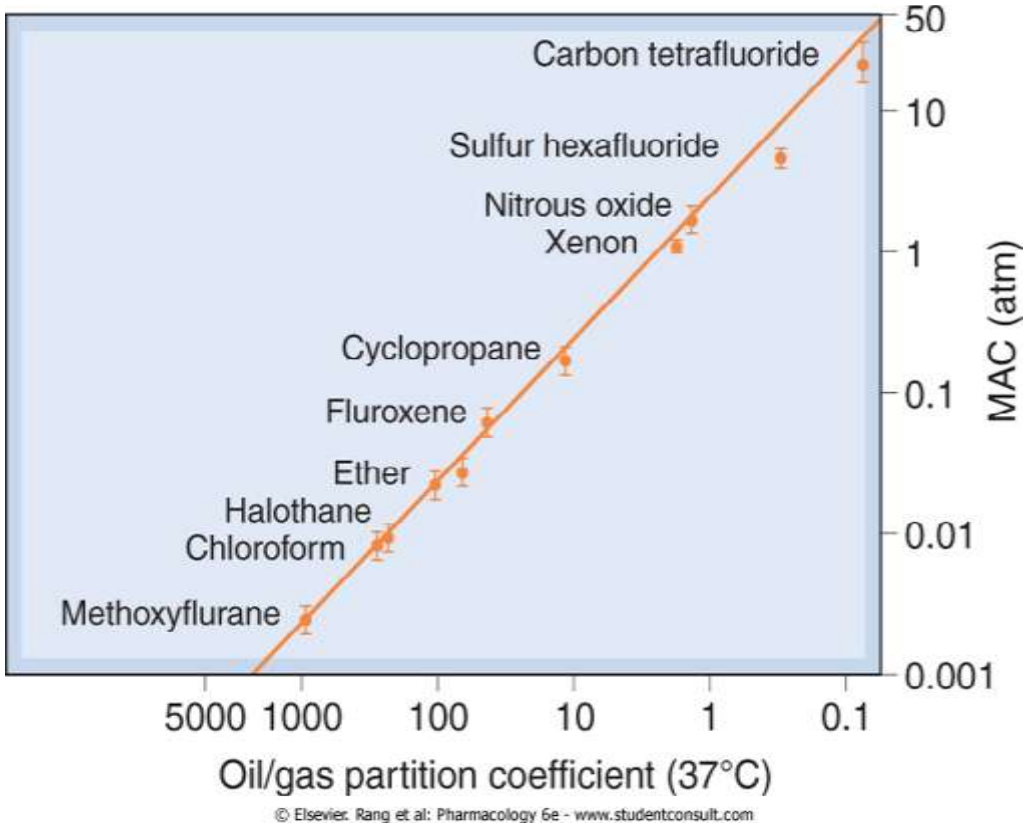


Figure 1:- Correlation **of anaesthetic potency with oil: gas partition coefficient.**

***EFFECTS ON ION CHANNELS*** :-

→ Following early studies that showed that anaesthetics can bind to various proteins as well as lipids, it was found that anaesthetics affect many ligand-gated ion channels.

→ Many anaesthetic agents are able, at concentrations reached during anaesthesia, to inhibit the function of excitatory receptors, such as the ionotropic glutamate, acetylcholine or 5-hydroxytryptamine receptors, as well as enhancing the function of inhibitory receptors such as $GABA_A$ and glycine . The $GABA_A$ receptor is the sole target for benzodiazepines and also appears to be a major target for intravenous anaesthetics, such

as **thiopental, propofol** and **etomidate** (see below), that act at a site on the receptor different from the benzodiazepine binding site.

→ Studies of experimentally mutated receptors have confirmed this and succeeded in identifying the specific 'modulatory sites' through which the anaesthetic drugs exert their effects on channel function. The 'two-pore domain' potassium channel known as TREK is another specifically anaesthetic-sensitive channel. It is activated, thus reducing membrane excitability, by low concentrations of volatile anaesthetics.

→ General anaesthetics inhibit excitatory channels (especially glutamate receptors) and facilitate inhibitory channels (particularly $GABA_A$ but also glycine and certain potassium channels), and these interactions are targeted at specific hydrophobic domains of the channel proteins. This is probably a serious oversimplification: as Little emphasises, individual anaesthetics differ in their actions and affect cellular function in several different ways, so a unitary theory is unlikely to be sufficient, but it does provide a useful starting point.

**Signs & Stages of Anesthesia :-**

The traditional description of the signs and stages of anesthesia (Guedel's signs) were derived from observations of the effects of diethyl ether, which has a slow onset of central action owing to its high solubility in blood. With these signs, anesthetic effects can be divided into four stages of increasing depth of central nervous system depression.

- **Stage of Analgesia:** The patient initially experiences analgesia without amnesia. Later in stage both analgesia and amnesia are produced.
- **Stage of Excitement:** During this stage, the patient often appears to be delirious and excited but definitely is amnesic. Respiration is irregular both in volume and rate, and retching and vomiting may occur. The patient may struggle and is sometimes incontinent. For these reasons, efforts are made to limit the duration and severity of this stage, which ends with the re-establishment of regular breathing.
- **Stage of Surgical Anesthesia:** This stage begins with the recurrence of regular respiration and extends to complete cessation of spontaneous respiration.

- **Four planes of stage III:** It have been described in terms of changes in ocular movements, eye reflexes, and pupil size, which under specified conditions may represent signs of increasing depth of anesthesia.
- **Stage of Medullary Depression:** This stage of anesthesia includes severe depression of the vasomotor center in the medulla as well as the respiratory center. Without full circulatory and respiratory support, death rapidly ensues.

**Classification:-**

**A. Inhalation:-**

1. **Gas:-** Ex. Nitrous Oxide
2. **Volatile Liquids:-** Ex. Ether, Halothane, Isoflurane etc.

**B. Intravenous**

1. **Inducing Agents:-** Ex. Thiopental Sodium, Propofol, Methohexitone Sodium etc.
2. **Slower acting drugs:-**
   - I. **Benzodiazepines:-** Ex. Diazepam, Lorazepam etc.
   - II. **Dissociative Anaesthetics:-** Ex. Ketamine
   - III. **Opioid Analgesia:-** Ex. Fentanyl

**DRUGS:-**

**INHALATIONAL ANAESTHETICS:-**

**UPTAKE AND DISTRIBUTION:-**

A few inhalational general anaesthetics are gases (e.g. nitrous oxide), but most are volatile liquids (e.g. sevoflurane) which are administered as vapours from calibrated vaporizers. None of the drugs in current use is flammable (unlike ether!). The anaesthetic vapours are carried to the patient in a mixture of nitrous oxide and oxygen or oxygen-enriched air. The concentration of an individual gas in a mixture of gases is proportional to its partial pressure. It is the partial pressure of an anaesthetic agent in the brain that determines the onset of anaesthesia, and this equates with the alveolar partial pressure of that agent. The rate of induction and recovery from anaesthesia

depends on factors that determine the rate of transfer of the anaesthetic agent from alveoli to arterial blood and from arterial blood to brain (Figure 2):

• *Anaesthetic concentration in the inspired air* – increases in the inspired anaesthetic concentration increase the rate of induction of anaesthesia by increasing the rate of transfer

into the blood.

• *Relative solubility in blood* – the blood:gas solubility coefficient defines the relative affinity of an anaesthetic for blood compared to air. Anaesthetic agents that are not very soluble in blood have a low blood:gas solubility coefficient, and the alveolar concentration during inhalation will rise rapidly, as little drug is taken up into the circulation. Agents with low blood solubility rapidly produce high arterial tensions and therefore large concentration gradients between the blood and brain. This leads to rapid induction and, on discontinuing administration, rapid recovery. Agents with higher solubility in blood are associated with slower induction and slower recovery.

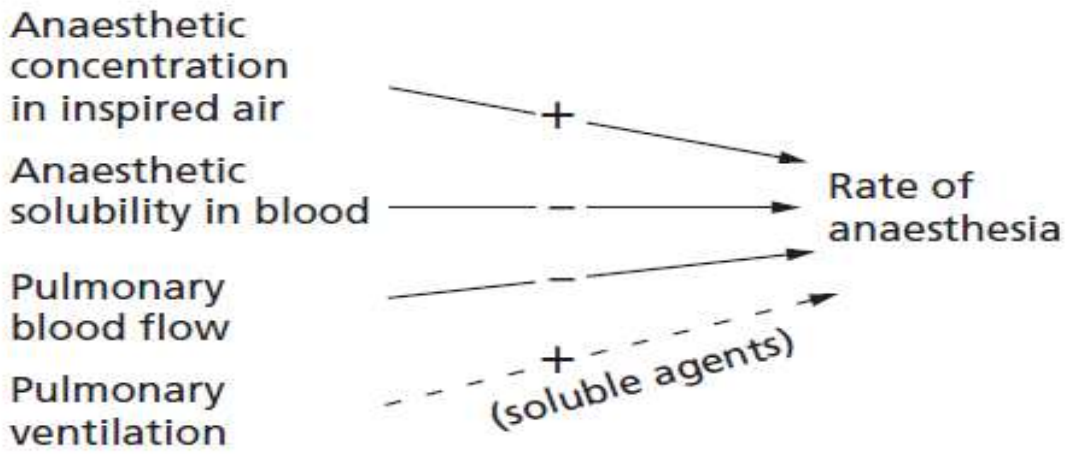


Figure 2: Factors determining the onset of action of inhalational anaesthetics.

*Pulmonary blood flow* – an increase in cardiac output results in an increase in pulmonary blood flow and more agent is removed from the alveoli, thereby slowing the rate of increase in arterial tension and slowing induction. A fall in pulmonary blood flow, as occurs in shock, hastens induction.

• *Pulmonary ventilation* – changes in minute ventilation have little influence on induction with insoluble agents, as the alveolar concentration is always high. However, soluble agents show significant increases in alveolar tension with increased minute ventilation.

• *Arteriovenous concentration gradient* – the amount of anaesthetic in venous blood returning to the lungs is dependent on the rate and extent of tissue uptake. The greater the difference in tension between venous and arterial blood, the more slowly equilibrium will be achieved.

**HALOTHANE** (FLUOTHANEI)

→ It is a volatile liquid with sweet odour, nonirritant and non inflammable. Solubility in blood is intermediate induction is reasonably quick and pleasant. It is delivered by the use of a special vaporizer

→ It is not a good analgesic or muscle relaxant; however, it potentiates competitive neuromuscular blockers.

→ Halothane causes direct depression of mvocardial contractility by reducing intracellular $Ca^{2+}$ concentration. Moreover, sympathetic activity fails to increase (as occurs with ether).

→ Cardiac output is reduced with deepening anaesthesia B. P starts falling early and parallels the depth. Many vascular beds dilate but total peripheral resistance is not significantly reduced. Heart rate is reduced by vagal stimulation, direct depression of SA nodal automaticity and lack of baro-receptor activation even when B.P falls. It tends to sensitize the heart to the arrhythmogenic action of Adr.

→ The electrophysiological effects are conductive to re-entry-tachyarrhythmias occur occasionally. Halothane causes relatively greater depression of respiration; breathing is shallow and rapid-PP of CO, in blood rises if respiration is not assisted. Ventilatory support with added oxygen is frequently required. lt tends to accentuate perfusion-ventilation mismatch in the lungs by causing vasodilatation in hypoxic alveoli.

→ Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate-preferred for asthmatics. It inhibits intestinal and uterine contractions. This

property is utilized for assisting exterual or internal version during late pregnancy. However, its use during labour can prolong delivery and increase postpartal blood loss.

**Pharmacokinetics**

→ Because of the relatively low blood:gas solubility, induction of anaesthesia is rapid but slower than that with isoflurane, sevoflurane and desflurane.

→ Excretion is predominantly by exhalation, but approximately 20% is metabolized by the liver.

→ Metabolites can be detected in the urine for up to three weeks following anaesthesia.

**Adverse effects**

→ *Cardiovascular*: ventricular dysrhythmias; bradycardia mediated by the vagus; hypotension; cerebral blood flow is increased, which contraindicates its use where reduction of intracranial pressure is desired (e.g. head injury, intracranial tumours).

→ *Respiratory*: respiratory depression commonly occurs, resulting in decreased alveolar ventilation due to a reduction in tidal volume, although the rate of breathing increases.

→ *Hepatic*. There are two types of hepatic dysfunction following halothane anaesthesia: mild, transient subclinical hepatitis due to the reaction of halothane with hepatic macromolecules, and (very rare) massive hepatic necrosis due to formation of a hapten–protein complex and with a mortality of 30–70%. Patients most at risk are middle-aged, obese women who have previously (within the last 28 days) had halothane anaesthesia. Halothane anaesthesia is contraindicated in those who have had jaundice or unexplained pyrexia following halothane anaesthesia, and repeat exposure is not advised within three months.

→ *Uterus*: Halothane can cause uterine atony and postpartum haemorrhage.

**Use**

→ Halothane is a potent inhalational anaesthetic. It is a clear, colourless liquid. It is a poor analgesic, but when co-administered with nitrous oxide and oxygen, it is effective and convenient. It is inexpensive.

→ Although apparently simple to use, its therapeutic index is relatively low and overdose is easily produced. Warning signs of overdose are bradycardia, hypotension and tachypnoea.

→ Halothane produces moderate muscular relaxation, but this is rarely sufficient for major abdominal surgery.

→ It potentiates most non-depolarizing muscle relaxants, as do other volatile anaesthetics.

**ISOFLURANE (Refered K.D.T)**

→ It is a later introduced, isomer of enflurane, has similar properties, but about one and half an hour times more potent, more volatile and less soluble in blood.

→ It produces relatively rapid induction and recovery and administered through a special vaporizer.

→ Cardiovascular Effects: Results fromStimulation of β adrenergic receptors. Isoflurane has a fall in B.P is similar to halothane, due to vasodilation while cardiac output well mainted. Heart rate increased.

→ It does not sensitize the heart to adrenergic arrhythmias. Coronary circulation is maintained safer in patients with myocardial ischemia (reduce blood supply to the heart muscles)

→ Cerebral blood flow is little affected, and uterine is relaxation is similar to halothane.

→ Isoflurane has muscle-relaxant properties and potentiates non-depolarizing muscle relaxants.

→ Respiration depression is prominent, Secretion are slightly increased.

→ Pupils donot dilate and light reflex is not lost even at deeper levels.

→ The rate of induction is limited by the pungency of the vapour. Fluoride accumulation is rare, but may occur during prolonged administration (e.g. when used for sedation in intensive care).

→ Metabolism of isoflurane is negligible. Renal and hepatic toxicity has not been encounterd. Post anaesthetics nausea and vomiting is low.

**DESFLURANE**

→ Desflurane is an inhalational anaesthetic. It has an MAC of 6% and a boiling point of 23.5°C, so it requires a special heated vaporizer. It has a blood:gas coefficient of 0.42 and therefore induction and recovery are faster than with any other volatile agents, allowing rapid alteration of depth of anaesthesia.

→ Cardiovascular stability is good. It cannot be used for inhalational induction because it is irritant to the respiratory tract.

**SEVOFLURANE**

→ Sevoflurane is a volatile liquid used for induction and maintenance of general anaesthesia. It has a blood:gas solubility coefficient of 0.6 and an MAC of 2%.

→ Cardiovascular stability during administration is a feature and it has gained popularity for rapid and smooth gaseous induction, with rapid recovery.

→ A theoretical disadvantage is that it is 3% metabolized producing fluoride. It may also react with soda lime. It is the inhalational anaesthetic of first choice for most indications.

**NITROUS OXIDE ($N_2O$):-**

→ It is colourless, odourless, heavier than air, non inflammable gas.

→ Nitrous oxide is a non-irritant gas which is compressed and stored in pressurized cylinders.

→ It is poor muscle relaxant, neuromuscular blockers are often required. Onset of $N_2O$ action is quick and smooth, recovery is rapid; both because of its low blood solubility.

→ Second gas effect and diffusion hypoxia occur with $N_2O$ only.

→ $N_2O$ has little effect on respiration, heart and blood pressure; breathing and circulation are better maintained with the mixture than with the potent anaesthetic given alone in full doses. It is non toxic to liver, kidney and brain.

→ It is analgesic, but only a weak anaesthetic.

→ It is commonly used in the maintenance of general anaesthetic in concentrations of 50–70% in oxygen in combination with other inhalational or intravenous agents.

→ It can reduce the MAC value of the volatile agent by up to 65%.

→ A 50:50 mixture of nitrous oxide and oxygen is useful as a self-administered dental and obstetric analgesic in labour.

**Pharmacokinetics**

→ Nitrous oxide is eliminated unchanged from the body, mostly via the lungs. Despite its high solubility in fat, most is eliminated within minutes of ceasing administration.

**Adverse effects**:

→ When nitrous oxide anaesthesia is terminated, nitrous oxide diffuses out of the blood into the alveoli faster than nitrogen is taken up. This dilutes the concentration of gases in the alveoli, including oxygen, and causes **hypoxia**. This effect is known as diffusion hypoxia, and it is countered by the administration of 100% oxygen for 10 minutes.

→ Nitrous oxide in the blood equilibrates with closed gas containing spaces inside the body, and if the amount of nitrous oxide entering a space is greater than the amount of nitrogen leaving, the volume of the space will increase. Thus pressure can increase in the gut, lungs, middle ear and sinuses. **Ear complications** and tension **pneumothorax** may occur.

→ Prolonged use may result in **megaloblastic anaemia** due to interference with vitamin B12 and agranulocytosis.

→ Nitrous oxide is a direct **myocardial depressant**, but this effect is countered indirectly by sympathetic stimulation.

**INTRAVENOUS ANAESTHETICS:-**

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec); are generally used for induction because of rapidity of onset of action.

**INDUCING AGENTS:-**

**THIOPENTAL SODIUM:-**

→ It is ultrashort acting thiobarbiturates, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection.

→ Extravasation of the solution or inadvertent intra-arterial injection produces intense pain-necrosis and gangrene may occur.

→ Injected i.v. as a 2.5 % solution, it produces unconsciousness in 15-20 sec.

→ Its undissociated form has high lipid solubility- enters brain almost immediately.

→ Distribution large amount of blood flow, vascular tissues.

→ Repeated injection, the extracerebral sites are gradually filled up-lower doses produce anaesthesia which lasts longer.

→ Disposal occurs mainly by hepatic metabolism.

→ Elimination half life 7-12 hr.

→ Poor Analgesics, painful procedures should not be carried out under its influence unless an opioid or N2O has been given; otherwise the patient may struggle, shout and show reflex changes in BP and respiration.

→ It is a weak muscle relaxant; does not irritate air passages.

→ Respiratory depression with inducing doses of thiopentone is generally transient, but with large doses it can be severe.

→ Blood pressures reduce immediately after injection mainly due to vasodilatation, but recovers rapidly.

→ Cardiovascular collapse (falls) may occur if hypovolemia shock or sepsis are present. It does not sensitize the heart to Adr, arrhythmias are rare.

→ It can be employed as the sole anaesthetic for short operations that are not painful.

**Adverse effects**

→ ***Central nervous system*** – many central functions are depressed, including respiratory and cardiovascular centres. The sympathetic system is depressed to a greater extent than the parasympathetic system, and this can result in bradycardia. **Thiopental** is not analgesic and at subanaesthetic doses it actually reduces the pain threshold. Cerebral blood flow, metabolism and intracranial pressure are reduced (this is turned to advantage when **thiopental** is used in neuroanaesthesia).

→ ***Cardiovascular system*** – cardiac depression: cardiac output is reduced. There is dilatation of capacitance vessels. Severe hypotension can occur if the drug is administered in excessive dose or too rapidly, especially in hypovolaemic patients in whom cardiac arrest may occur.

→ ***Respiratory system*** – respiratory depression and a short period of apnoea is common. There is an increased tendency to laryngeal spasm if anaesthesia is light and there is increased bronchial tone.

→ ***Miscellaneous adverse effects*** – urticaria or anaphylactic shock due to histamine release. Local tissue necrosis and peripheral nerve injury can occur due to accidental extravascular administration. Accidental arterial injection causes severe burning pain due to arterial constriction, and can lead to ischaemia and gangrene. Post-operative restlessness and nausea are common.

→ **Thiopental** should be avoided or the dose reduced in patients with hypovolaemia, uraemia, hepatic disease, asthma and cardiac disease. In patients with porphyria, **thiopental** (like other barbiturates) can precipitate paralysis and cardiovascular collapse.

**KETAMINE**

→ **Ketamine** is chemically related to **phencyclidine** (still used as an animal tranquillizer, but no longer for therapeutic use in humans because of its psychogenic effects and potential for abuse), and produces dissociative anaesthesia, amnesia and profound analgesia.

→ It is a relatively safe anaesthetic from the viewpoint of acute cardiorespiratory effects since, unlike other intravenous anaesthetics; it is a respiratory and cardiac stimulant.

→ A patent airway is maintained and it is a bronchodilator. Because of its ease of administration and safety, its use is widespread in countries where there are few skilled anesthetists. It has been used for management of mass casualties or for anaesthesia of trapped patients to carry out amputations, etc.

→ It is used in shocked patients, because unlike other intravenous anaesthetics it raises rather than lowers blood pressure. An intravenous dose produces anaesthesia within 30 – 60 seconds, which lasts for 10–15 minutes.

→ An intramuscular dose is effective within three to four minutes, and has duration of action of 15–25 minutes.

→ There is a high incidence of hallucinations, nightmares and transient psychotic effects. Children cannot articulate such symptoms and it is disturbing that it is still used particularly in this age group.

**Adverse effects**

→ Psychosis and hallucinations are common.

→ Intracranial pressure is increased by ketamine.

→ Blood pressure and heart rate are increased.

→ Salivation and muscle tone are increased.

→ Recovery is relatively slow.

**BENZODIAZEPINES: - (BZDS)**

→ **Midazolam** is a water-soluble benzodiazepine and useful intravenous sedative. It has a more rapid onset of action than **diazepam** and a shorter duration of action, with plasma half-life of 1.5–2.5 hours.

→ Dose is titrated to effect. **Midazolam** causes amnesia, which is useful for procedures such as endoscopy or dentistry.

→ The use of benzodiazepines for induction of anaesthesia is usually confined to slow induction of poor-risk patients. Prior administration of a small dose of **midazolam** decreases the dose of intravenous anaesthetic required for induction.

→ Large doses can cause cardiovascular and respiratory depression. Repeated doses of **midazolam** accumulate and recovery is prolonged.

→ **Diazepam** is used for premedication (oral), sedation (by slow intravenous injection) and as an anticonvulsant (intravenously). A preparation formulated as an emulsion in soyabean oil has reduced thrombophlebitis from intravenous **diazepam**.

**OPIOIDS ANALGESICS:-**

→ High-dose opioids are used to induce and maintain anaesthesia in poor-risk patients undergoing major surgery. Opioids such as **fentanyl** provide cardiac stability. Onset is slow and the duration of action prolonged so that ventilatory support is required post-operatively. Addition of a small dose of volatile anaesthetic, benzodiazepine or **propofol** is required to avoid awareness during anaesthesia.

→ High-dose opioids can cause chest wall rigidity interfering with mechanical ventilation. This can be prevented by muscle relaxants.

**FENTANYL**

→ **Fentanyl** is a synthetic opioid and is the most commonly employed analgesic supplement during anaesthesia. It is very lipid soluble and has an onset time of one to two minutes. It has approximately 100 times the analgesic activity of **morphine**.

→ **Fentanyl** is rapidly and extensively metabolized, the $t_{1/2}$ being two to four hours, the short duration of action (the peak effect lasts only 20–30 minutes) being explained by redistribution from brain to tissues.

→ Depression of ventilation can occur for several minutes.

→ **Fentanyl** and the other potent opioids must not be used in situations where ventilation cannot be controlled.

→ **Fentanyl** has little cardiovascular effect, but bradycardia may occur. Neuroleptanalgesia is produced by a combination of a butyrophenone (**droperidol**) and an opioid (**fentanyl**).

→ It is a state of inactivity and reduced response to external stimuli, sometimes used for complex diagnostic procedures.