REVIEW OF LITERATURE
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In the mid seventeenth century, soon after the description of the circulatory system by Harvey (1628), Percival Christopher Wren and Daniel Johan Major (1665) conceived the idea of injecting medicinal compounds directly into the blood and performed the first experiment. Wren injected the opium solution into the venous system of a dog by means of a quill fastened to bladder. The injection "stupefied" the dog with in a short time without killing it.

Pierre-Cyprian Ore (1872) is regarded as the true pioneer of intravenous anaesthesia. He used chloral hydrate intravenously to produce anaesthesia. But several unfortunate post operative deaths conspired against the acceptance of this method.

This followed another hiatus of 33 years. The process was started again by Krawkow (1905), who injected Hedonal (methyl-propyl-carbinal-urethane). Four years later Burkhardt popularised the intravenous use of Diethyl ether and Chloroform.

Neol and Souttar (1913) reported the use of intravenous paraldehyde followed by MgSO₄ (1916).

Nakagawa (1921) used Alcohol intravenously to induce surgical anaesthesia.

Barbituric acid was synthesized by Baeyer (1864), but its narcotic effect was not discovered. Later barbutric acid (Veronal) was synthesized by
Father of intravenous anaesthesia, Helmeet Weese (1932) used Hexobarbitone. It was the first drug to make intravenous anaesthesia popular.

Sodium Pentothal, ultra short acting hypnotic synthesized by Ernest Henry Volwiler and Dorothee Turben (1932) was first introduced into clinical practice by Lundy and Waters in 1934. Although Lundy published the first report, but it is Waters to whom belongs the distinction of first clinical administration of Thiopentone in man. Its fate in the body and distribution was described by Brodie (1950). But unfortunately due to lack of an understanding of its pharmacokinetics, it was used in the same manner as diethyl ether and chloroform for the induction and maintenance of general anaesthesia and resulted in disasters including hypotension and prolonged sleeping times. It also lead to the casualties at Pearl Harbour resulting in so many deaths that intravenous Thiopentone was described as ‘an ideal drug for “EUTHANASIA”’. An understanding of its pharmacokinetics and its desirable pharmacological properties made Thiopentone the standard anaesthetic drug to induce anaesthesia, but certain adverse effects like cardiovascular and respiratory depression, somnolence, psychic problems, motor disturbances, anaphylaxis, bronchospasm, cough, hiccups, nausea and risk with intra arterial injection mar its popularity as an ideal induction agent.

After Thiopentone sodium, many inducing agents were introduced with many side effects like Eugenol Derivatives (Propanadid) which is oil base compound causing increased incidence of phlebitis and release of
histamine causes allergic reaction, with Althesin anaphylactoid reaction, with Etomidate which is also oil base compound produces local pain, Diazpam also produces thrombophlebitis and with ketamine psychic emergence.

Propofol is the most recent intravenous anaesthetic was introduced into clinical practice by Kay and Rolly in 1977, who confirmed the potential of Propofol as an anaesthetic induction agent. Because of its rapid onset of action, short duration with rapid and clear-headed emergence and lack of cumulative effect, it reduces pressure on post operative facilities, with less incidence of nausea and vomiting in comparison to any other inducing agent.

A brief review of the pharmacokinetics and pharmacodynamics of Thiopentone and Propofol would therefore not be out of place before a discussion of there effect and utility as induction agents in clinical obstetric.
Thiopentone is a derivative of barbituric acid (2-4, 6 trioxohexa hydro pyrimidine). It is an ultra short acting barbiturate. It differs from its predecessor pentobarbitone in having a sulphur atom rather than oxygen attached to one carbon atom resulting in more rapid induction and recovery.

\[
\begin{align*}
\text{CH}_3\text{(CH}_2\text{)} &
\quad \text{O} \\
\text{CH}_3\text{(CH}_2\text{CH} &
\quad \text{N} \\
\text{CH}_3 &
\quad \text{S}
\end{align*}
\]

5 ETHYL-5(1-METHYL – BUTYL) – 2-THIOBARBITURIC ACID

**MECHANISM OF ACTION**

Sedative hypnotic effect of Thiopentone is due to enhancement of action of GABA, while GABA mimetic effect i.e. directly activating chloride channel at slightly higher concentration may be responsible for barbiturate anaesthesia.
PHYSICAL PROPERTIES

The drug is used in the form of its sodium salt. Sodium Thiopentone is a pale yellow amorphous powder with a bitter taste and slightly sulphurous smell. Thiopentone is supplied in vials 0.25 g, 0.5 g or 1.0 g. Thiopentone is a weak acid and its pKa is 7.60 and has optimal aqueous solubility at high pH values. At physiological pH, it is slightly more than half in the nonionised state. The commercial preparations contain sodium carbonate which prevent precipitation of the free acid by atmospheric CO₂ and results in an alkaline solution (pH - 10.5 - 11.0), solution is made 2.5% and it is stable for 1 week if refrigerated.

Hypnotic activity is introduced into barbituric acid molecule by the addition of side chains, especially if at least one of them is branched in position 5. The length of the side chain in the 5 position influences both the potency and duration of action of the barbituric acid derivatives. Replacing the oxygen atom with a sulphur atom at position 2 of an active barbiturate produces a barbiturate, with a more rapid onset and a shorter duration of action :- the thiobarbiturates. Methylation of an active barbiturate in position increases incidence of excitatory side effects.

Thiopental exists in 2 type of isomer (l) and (d) because of presence of asymmetric carbon atoms in one of the side chains attached to carbon 5 of the barbiturate ring. The (l) isomer is nearly twice as potent as the (d) isomers despite their similar access to the central nervous system.
When administered intravenously, on first circulation, much of the drug is taken up from the injected bolus by tissues of high blood flow particularly the central nervous system and vital organs kidney, liver. The rate of drug transfer is very fast because of Thiopentone's lipophilic property and this correlates with its rapid onset of anaesthetic action. Peak level in vessel rich tissue is reached in 1-2 min, because of its high solubility (partition coefficient) it diffuses rapidly into brain and subsequent slower transfer of the drug from the plasma occurs to other tissues which are less well perfused, first to muscle and later to fat depots. Such that plasma drug concentrations fall markedly and quickly, equilibrium with the muscle does not occur for about 15 min after administration. Although Thiopentone sodium is lipid soluble but because of poor vascularity of fat, concentration of drug increases in fat lately over about 2 hours. As the drug leaves the CNS for the periphery, recovery of consciousness ensues. At this time, most of the injected drug dose is still present in the body, nearly redistributed to the tissues. Eventually, sequestration occurs to fat depots, where the drug remains for many days in equilibrium with the relatively minute quantity in the plasma.

In the plasma, Thiopentone is bound with protein, predominantly albumin, to a normal extent of 70-80%. At high concentration of drug, the proportion bound is markedly reduced.

This binding limits the concentration of Thiopentone in free solution which is readily available for transfer to the brain in old age and in severe liver disease or malnutrition, where protein binding is impaired due to
hypo-proteinemia. More drug is available for transfer and an exaggerated anaesthetic response may result. In such circumstances, Thiopentone should be given in appropriately smaller dose. Drug which binds with proteins potentiate the effect of Thiopentone. Thus sulphafurazole and probenecid both exaggerate the response to standard dose of Thiopentone.

Thiopentone is eliminated almost entirely after metabolic degradation in the liver, less than 0.5 percent being excreted unchanged in the urine. Hepatic extraction ratio is 0.1 – 0.2. Metabolism renders the molecule less lipid and more water soluble, thus depriving it the biological activity and redenerg it less readily reabsorbed in the renal tubules. The pathways involved in the liver is three fold

1. Side – chain oxidation at C₅
2. Oxidation replacement of sulphur at C₂ to form a small quantity of the drug’s oxy equivalent, Pentobarbitone.
3. Ring cleavage to form urea and a three carbon fragment.

Hepatic dysfunction slows elimination and can prolong recovery, though only after large doses.

The rate at which distribution and elimination occurs into three exponentials which represent distribution to high blood flow area (α₁) distribution to low blood flow areas such as fat (α₂) and elimination (β). Thus half lives in young healthy patients with in the ranges

\[
\begin{align*}
\alpha_1 &= 1.7 \text{ to } 6.5 \text{ min.} \\
\alpha_2 &= 23 \text{ to } 71 \text{ min.} \\
\beta &= 5 \text{ to } 10 \text{ hrs.}
\end{align*}
\]
True drug elimination is therefore very slow, a total body clearance is high (82 - 288 ml/min) indicating that the reason underlying slow elimination is the large distribution volume which makes most of the drug inaccessible to the liver for its breakdown.

There are two important practical consequences of the prolonged elimination of Thiopentone:

1. The residual effects of even a small single dose will persist for many hours, reducing mental anxiety and having an additive effect with other sedatives.

2. The use of repeated small doses or infusion results in cumulation in adipose tissues and persistent effects for many days.

The usual induction dose is 4-5 mg/kg, for healthy adults.

Interpatient variability in the dose requirement for female can be calculated by formula:-

Dose (mg) = 300 + weight - 2 x Age - 50

FACTORS INFLUENCING PHARMACOKINETICS

Pregnancy: Pregnancy has little influence on the pharmacokinetics of Thiopentone and although the clearance is greater in pregnant patients, the elimination half-life is longer. The drug diffuses freely across the placental barrier but the rapid redistribution in the maternal tissues between induction of anaesthesia and delivery is a major factor in producing a more alert baby than the mother’s state would suggest. Certainly the umbilical venous plasma concentrations, which should be similar to those entering the fetal
anaesthesia in adults.

**Obesity**: Patient have greater volume of distribution so longer terminal half time, also greater clearance but difference becomes insignificant if values are normalised by body weight.

**Rate of Administration**: Slow injection rate are associated with a reduced incidence of apnoea and a significant decrease in arterial pressure. Rapid injection is associated with increased number of side effects.

**Drug plasma protein binding**: Hypoproteinemia in case of renal failure or malnutrition or due to any other cause results in reduced plasma binding of drug, so required induction dose is reduced. But clearance and elimination of the drug is unchanged in case of renal failure and affected only with very high doses in cirrhosis.

**pH of Blood**: Acidosis reduces the Thiopentone concentration in the plasma by up to 40%.

**Age**: Increasing age is associated with lower induction dose of Thiopentone because of lower cardiac output and failure to compensate for the effects of the drug on the circulation.

**PHARMACODYNAMICS**

1. **Central Nervous System**: Thiopentone rapidly crosses the blood brain barrier and the concentration in the CSF, reaches a level almost as high as that of the unbound drug in the plasma. It causes sedation, hypnosis, anaesthesia and
respiratory depression like other barbiturates depending on the dose and rate of injection. There is an anticonvulsant action also. It produces progressive depression of the CNS. The cerebral cortex and ascending reticular activating system are depressed before the medullary centres. In clinical practice this is produced so rapidly that the classical signs of anaesthesia are of no value. Although respiratory depression is marked, patient with apnoea may yet react to a surgical stimulus.

Cerebral metabolic rate fall by about 50%, cerebral blood flow is reduced by 30-50%. In addition reduction in cardiac output and arterial blood pressure lead to secondary effects on cerebral perfusion. CSF pressure is also reduces. Thiopentone in dose insufficient to cause unconsciousness is antanalgesic and this sensitivity to pain lasts into the post operative period.

**Acute tolerance:** is seen with Thiopentone. There is a relationship between the induction dose of Thiopentone and the blood Thiopentone level at which patients awake from anaesthesia. The greater the induction dose, the greater will be the increments of drug required to maintain surgical anaesthesia. Because of acute tolerance it is difficult to correlate blood levels with depth of anaesthesia but about 7 µg/ml is an average level.

Return of normal mental faculties does not accompany apparent return of consciousness. Patient must not drive a car or engage in responsible activity for 24 hrs.

2) **CARDIOVASCULAR SYSTEM**:–

Under light anaesthesia, there is wide spread dilatation of the muscle and skin vessels but no obvious alteration in the total peripheral resistance. The increase in peripheral flow is compensated by constriction of the
output remains relatively unchanged.

In contrast, the rapid induction with bolus dose causes a reduction in arterial blood pressure, left ventricular stroke work index, pulmonary wedge pressure with marked peripheral vasodilatation. Peripheral vasodilatation causes pooling of blood in the extremities and reduction of the venous return to the heart leading to decrease in cardiac output. There is some degree of tachycardia (10-20%) which with lower doses contribute to maintenance of the blood pressure and cardiac output.

Higher doses of it causes increasing myocardial depression and vasodilatation but tolerable with normal cardiovascular system.

Dysrhythmias occurs in a proportion of cases and are usually ventricular extrasystoles. The ability to compensate these changes is impaired in hypovolemic patients, so induction is hazardous in patients with compensated shock states. Also in patients with treated hypertension, heart can not compensate so Thiopentone induction may be dangerous. Patient with fixed cardiac output as with mitral stenosis, cardiac tamponade also required slow administration of the drug with careful assessment of anaesthetic depth.

3) **RESPIRATORY SYSTEM**:

Thiopentone in common with other barbiturates is a potent respiratory depressant, that it depress the spontaneous respiratory rate and depth and depress the sensitivity of the respiratory centre to CO₂. In deep anaesthesia with Thiopentone respiratory drive is maintained largely by the carotid sinus and is related to hypoxia. Depression of respiratory centre is antagonised by
surgical stimuli and potentiated by opioids, depending on the dose and rate of injection. The usual sequence of events when a dose of Thiopentone is given slowly is for a few deeper breaths to be taken just prior to the loss of consciousness. There may be a brief period of apnoea due to direct effect of Thiopentone on respiratory centre coinciding with a low CO₂ tension from the preceding deep breaths. Respiration returns gradually and then further fade away as more Thiopentone is given.

During light anaesthesia, there is heightening of the laryngeal reflexes so that minor stimuli, local or remote may cause laryngospasm. If predisposing factor as sensitive bronchial tree in asthma or stimulation of the larynx by mucus is present, the patient may develop bronchospasm or laryngospasm but Thiopentone does not it self cause these conditions so it is preferable to avoid Thiopentone in asthmatic patient. Cough and hiccup are uncommon during induction with Thiopentone

4) **LIVER AND KIDNEY** :-

There is no evidence that Thiopentone adversely affects liver function unless hypoxia is present in conventional induction doses. There is transient impairment of liver function following large doses and infusions. Blood glucose concentrations are unaltered.

The effects of Thiopentone on the kidneys are secondary to its actions on the circulation. It causes liberation of antidiuretic hormone so that urine output during Thiopentone anaesthesia is decreased.

5) **ALIMENTARY SYSTEM** :-

Some depression of intestinal motility occurs but soon return to normal when patient is awake.
Pupils first dilate, then contract. Sensitivity to light remains until the patient is deep enough to permit incision of the skin and at this stages, the eyeballs are usually centrally placed. Intraocular pressure is reduced. Loss of eyelash reflex is a sign of induction of anaesthesia.

7) **REPRODUCTIVE SYSTEM** :-

In therapeutic doses, Thiopentone does not alter the tone of the gravid uterus or motility of the fallopian tubes. It rapidly crosses the placental barrier. Thiopentone is not harmful to the fetus when the drug is given for anaesthetic induction for caesarean in doses upto 6 mg/kg, but 8 mg/kg does depress the fetus. Placental circulatory factors and redistribution of Thiopental in the mother and fetus protect the fetal brain and spinal cord from high concentrations of barbiturates. Safe delivery of the fetus by caesarean section is possible if accomplished within 10 minutes after anaesthetic induction with Thiopentone.

8) **PORPHYRIA** :-

Porphyrin is a pigment formed in the liver from aminolaevulinic acid, a process catalysed by aminolaevulinic acid synthetase. Thiopentone stimulate aminolaevulinic acid synthetase enzyme so causing increasing in porphyria level which is already elevated in patient with porphyria. All types of porphyria are not adversely affected by Thiopentone but danger is so serious that Thiopentone is absolutely contraindicated in these patients. Thiopentone precipitates acute attack of porphyria.
LOCAL EFFECTS

Pain on injection and venous irritation are rare even when injected into small veins.

Venous thrombosis occur in about 3-4% cases. Rest to the affected part is the best treatment.

If injected subcutaneously in large volumes can cause tissue damage. Urticarial rash and anaphylactoid reaction can also occur.

The serious danger with Thiopentone is intra-arterial injection but reduced by the routine use of 2.5% solution.

Injection into artery lead to precipitation of crystals of insoluble Thiopentone and haemoglobin in the smaller vessels of the limb. ATP is then released leading to intimal damage and intravascular thrombosis. Immediately on injection the patient complains of intense pain and radial pulse may disappear as arterial system undergoes generalised spasm due to release of noradrenaline. Avoidance is most readily achieved by awareness of danger and knowledge of aberrant arteries. Treatment includes leaving the needle or cannula in site, use of saline, lignocaine, papaverine in to the same vessel to encourage vasodilatation. Brachial plexus block can be performed to remove other vasoconstrictor influences.

Thiobarbiturates cause histamine release, but not by oxybarbiturate.
In pregnancy there is a high cardiac output state, decrease in peripheral resistance, decrease in blood pressure and increase blood flow to the uterus. And also increase in blood volume and decrease in plasma protein but increase in total amount. These physiological changes of pregnancy lead to rapid onset of action of Thiopentine, less hypotensive effect, increased drug binding, less drug is required for induction as compare to non pregnant and slow elimination from the body although the clearance is greater therefore prolong somnolence. Rapid redistribution in the maternal tissue between induction of anaesthesia and delivery is a major factor in producing a more alert body than the mother state would suggest certainly the umbilical venous plasma concentrations which should be similar to those entering the fetal brain, were well below the arterial plasma concentration required to produce anaesthesia in adults. Thiopentine, being highly lipid soluble, crosses the placenta readily, but frequently does not have the expected profound effects in the neonate that might be expected because of the short interval between its administration for induction of anaesthesia and delivery of the infant. But in large dose (8mg/kg) does depress the fetus, and is not harmful to foetus when the drug is given for anaesthetic induction for caesarean section in doses up to 6mg/kg Thiopentone cause less awareness and due to its slow elimination from body prolong somnolence occur.
(1) **ABSOLUTE:**  
   i) Prophyria – Not all type of porphyria, but danger is so great that risk can not be taken.  
      It causes precipitation of acute attack.  
   ii) Patient with history of Thiopentone anaphylaxis.

(2) **RELATIVE:**  
   Special care is needed in these cases –

   (a) Shocked, debilitated, severely anaemic and uraemia cases small dose are required.

   (b) Patients with gross dyspnoea due to cardiac and respiratory disease, in fixed cardiac output disease.

   (c) Patients with respiratory obstruction or status asthmatic.

   (d) Patient with difficult veins
Propofol (Diprivan) is the most recent intravenous anaesthetic to be introduced into clinical practice by Kay and Rolly in 1977.

**PHYSICOCHEMICAL CHARACTERISTICS**

Propofol is 2, 6-di-iso-propyl-phenol. It is one of a group of alkyl-phenols that have hypnotic properties. The alkyl-phenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble. The present formulation is in a 1 percent (wt/vol) emulsion of 10 percent soya bean oil, 1.2 percent purified egg phosphatide and 2.25 percent glycerol. This is similar to the fat emulsion Intralipid which is used for parenteral nutrition. Propofol has a pH of 7 and appears as a slightly viscous, milky white substance. Propofol is available as 1 percent solution in 10 ml and 20 ml vials. 20 ml clear glass ampules, 50 and 100 ml vials and in 50 ml prefilled syringes. It is stable at room temperature and is not light sensitive. If a dilute solution of Propofol is required, it is compatible with 5 percent dextrose in water.

![](image)

PROPOFOL (2,6 di-iso Propyl-Phenol)
DOSAGE

The usual induction dose is 1.5 – 2.5 mg/kg

METABOLISM

Propofol is rapidly metabolised in the liver by conjugation to glucuronide and sulfate to produce water-soluble compounds, which are excreted by the kidneys. Less than 1 percent Propofol is excreted unchanged in urine, and only 2 percent is excreted in faeces. The metabolites of Propofol are thought not be active. Because clearance of Propofol exceeds hepatic blood flow, extra hepatic metabolism or extrarenal elimination has been suggested. Propofol itself results in a concentration dependent inhibition of cytochrome P-450 and thus may alter the metabolism of drugs dependent on this enzyme system.

PHARMACOKINETICS

Propofol is 98 percent protein bound and, being highly lipophilic, is distributed rapidly throughout the blood and vessel rich tissues. Blood level then decline with the initial distribution half life of 2 to 8 minutes and elimination half life has varied from 1.0 to 3 hours. Other worker have identified three compartment model of initial and slow distribution half lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half life of 4 to 23.5 hours. The clearance of Protocol is extremely high – 1.5 to 2.2 L/min. which accounts for the rapid wakening from anaesthesia.

The pharmacokinetics of Propofol may be altered by a variety of factors (e.g. gender, weight, pre existing disease, age and concomitant medication). Propofol may alter its own clearance by decreasing hepatic
Propofol is primarily a hypnotic. It acts by promoting the function of the $\beta_1$ subunit of GABA through activation of the chloride channel and thereby enhancing inhibitory synaptic transmission. It also inhibit the NMDA sub type of glutamide receptor through modulation of channel gating.

Propofol is not antianalgesic.

The onset of hypnosis following doses of 2.5 mg/kg is rapid (one arm brain circulation), with a peak effect seen at 90 to 100 seconds. $ED_{50}$ of Propofol is 1 to 1.5 mg/kg following a bolus. The duration of hypnosis is dose dependent, being 5 to 10 minutes following 2 to 2.5 mg/kg.

In subhypnotic doses, Propofol provides sedation and amnesia. Propofol tends to produce a general state of well being. Recovery after Propofol 2.5 mg/kg is significantly faster. Propofol has a direct anticonvulsant effect which is dose dependent. Tolerance has been developed to Propofol following either repeat anaesthesia or prolonged infusion (days).

Propofol decreases intracranial pressure (ICP) in patient with normal or increased intracranial pressure. Normal cerebral reactivity to CO$_2$ and
cerebral metabolic rate of oxygen consumption (CMRO₂) by 36 percent. It also provide cerebral protective effects following an acute ischaemic insult.

**EFFECT ON THE RESPIRATORY SYSTEM**

Propofol is a potent respiratory depressant similar to barbiturates. Apnea occurs after an induction dose of Propofol; the incidence and duration of apnea appear to be dependent on dose, speed of injection and concomitant premedication. The onset of apnea is usually preceded by marked tidal volume reduction and tachypnea. Following induction dose it decreases respiratory rate significantly for 2 minutes and minute volume is significantly reduced for up-to 4 minutes.

The ventilatory response to CO₂ is also decreased during a maintenance infusion of Propofol. Propofol (1.5 – 2.5 mg./kg), results in an acute (13 – 22%) rise in Paco₂ & decrease in pH. Propofol (50 – 120 mg kg min) also depress the ventilatory response to hypoxia.

Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease.

**EFFECT ON THE CARDIOVASCULAR SYSTEM**

The most prominent effect of Propofol is a decrease in arterial blood pressure during induction of anaesthesia. Independently of the presence of cardiovascular disease an induction dose of 2-2.5 mg/kg produces a 25 – 40 percent reduction of systolic blood pressure. Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index (≈15%), stroke
volume index (≈20%) and systemic vascular resistance (15–25%). Left ventricular stroke work index is also decreased (by ≈ 30%). The decrease in systemic pressure following an induction dose of Propofol appears to be due to both vasodilation and myocardial depression. Both the myocardial depressant effect and the vasodilation appear to be dose dependent and plasma concentration dependent. The vasodilatory effect of Propofol appears to be due both to a reduction in sympathetic activity and to a direct effect on intracellular smooth muscle calcium mobilization.

Heart rate does not change significantly after an induction dose of Propofol. As Propofol either resets or inhibits the baroreflex, thus reducing the tachycardia in response to hypotension. Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction.

Heart rate may increase, decrease or remain unchanged when anaesthesia is maintained with Propofol. As the vasodilatory and myocardial depressant effects are concentration dependent, the decrease in BP from Propofol during the infusion phase is much less than that seen following an induction bolus. An infusion of Propofol results in a significant reduction in both myocardial blood flow and myocardial oxygen consumption therefore the global myocardial O₂ supply/demand ratio is preserved.

**OTHER EFFECTS**

Propofol does not potentiate neuromuscular blockade produced by both nondepolarizing and depolarising neuromuscular blocking agents. Propofol produces no effect on the evoked electromyogram or twitch tension; however, good intubating conditions after Propofol alone have been
Propofol does not trigger malignant hyperpyrexia and is the anaesthetic of choice in patients with this condition.

Propofol following a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to ACTH stimulation. Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function.

Propofol also possess significant antiemetic activity at low doses. Propofol at subhypnotic doses has also relieved cholestatic pruritus and was effective as naloxone in treating pruritus induced by spinal opiates.

Propofol cause a dose dependent decrease in the thermoregulatory threshold for vasoconstriction, but it has little effect on the sweating threshold.

Propofol only decreases polymorphonuclear leukocyte chemotaxis but not adherence phagocytosis and killing.

Propofol, an Induction agent in obstetric patients :-

Propofol is highly lipid soluble, has rapid onset of action, readily crosses the placenta and can cause foetal depression but is safe for foetus if induction to delivery time is less than 10 minutes. The clearance of it is extremely high. Therefore recovery from anaesthesia is rapid with clear headed emergence. It causes decrease in arterial blood pressure cardiac output/cardiac index, stroke volume index and systemic vascular resistance during induction leading to maternal hypotension so can lead to foetal hypoxia but these effects are less because of physiological change during pregnancy that is increase cardiac out put increase in blood volume and
increase in total body water compensates the hypotensive effect of Propofol. Propofol has antiemetic effect so very less chance of post operative nausea and vomiting. Propofol causes awareness during induction.

**SIDE EFFECTS**

Pain on injection can be found with administration of Propofol. It is reduced by using a large vein, avoiding veins in the dorsum of hand, adding lidocaine to the Propofol solution and giving along with 5% Dextrose infusion.

Myoclonus can occur after induction with Propofol. Apnoea following induction with Propofol is common.

Decrease in systemic blood pressure, is the most significant side effect on induction with Propofol.

Slow administration and lower doses in adequately prehydrated patients may attenuate the decrease in arterial pressure.

1. Kosaka Y., et al (1969) studied the intravenous thiopental anaesthesia for caesarean section, they concluded that Thiopentone is not harmful to the fetus when the drug is given for anaesthesia induction for caesarean section in doses up to 6 mg/kg, but 8 mg/kg does depress the fetus.

2. Hulton et al (1978) evaluated that Methohexitone and low dose ketamine appear to offer reasonable alternative to Thiopentone for anaesthetic induction at caesarean section.
plasma binding of thiopental in pregnant women going for caesarean section. They concluded that apparent volume of distribution, volume of distribution at steady state and elimination, half life are significantly greater at caesarean section and that systemic plasma clearance show a similar trend as comparison with non pregnant patient receiving Thiopentone for induction. They demonstrated that difference in maternal distribution and elimination characteristics of Thiopentone may be more important determinants of inter subject differences in fetal drug exposure than difference in dose or elimination half life.

4. Bernstein K. et al (1985) studied the influence of two different anaesthetic agents on the newborn and the correlation between foetal oxygenation and induction delivery time in elective caesarean section. They concluded that safe delivery of the fetus by caesarean section is possible if accomplished within 10 minutes after anaesthetic induction with either thiopental or Ketamine.

5. Gaspari F. et al (1985) studied the elimination kinetics of Thiopentone in mothers and their newborn infants. He resulted that at delivery, 4-9 min after induction, drug concentrations in cord blood were half those in maternal blood. The mean half – life of Thiopentone in the first renal clearance of Thiopentone was estimated in the newborn ; 0.074 ml/h/kg. Only 0.0007% (about 2 micrograms) of the maternal dose was recovered in the urine of newborn over 36h.
Thiopentone (4 mg kg⁻¹) to induce anaesthesia for caesarean section in 62 normotensive patients. During induction and before laryngoscopy, blood pressure did not change in either group, when laryngoscopy and intubation were performed mean blood pressure of both patient group increased 20-30 percent, with Ketamine heart rate was unchanged from pre-induction rate of 85 beats/min before laryngoscopy and increased significantly by 15 percent during laryngoscopy and intubation, with Thiopentone heart rate increased significantly to 20 percent during induction and increased further to 35 percent during laryngoscopy and intubation, Neonatal outcome was good and did not differ significantly between groups.

7. Bland B.A. et al (1987) administered 0.2 mg/kg Midazolam or Thiopental 3.5 mg/kg, with succinylcholine 1 mg/kg for rapid sequence induction in sixty healthy mothers undergoing elective caesarean section randomly. Maintenance of anaesthesia was identical in all patients. Haemodynamic responses were similar as were the biochemical status of mothers and infants. However 1 minute Apgar minus color (A-C) scores less than 5/8 (representing 'severe' neonatal depression) were recorded in five infants after midazolam so it is concluded that midazolam is less suitable than Thiopental for induction in patients undergoing caesarean section.

8. Baraka A. et al (1989) concluded that awareness was significantly greater induction with Thiopentone (70 percent) than after Ketamine (13.3%) in patients undergoing caesarean section.
vein blood gas values in the new borns.

9. Bach V. et al (1989) studied placental transfer and elimination of Midazolam and Thiopentone in neonates delivered by mothers who were induced by Midazolam or Thiopentone. Placental transfer of Thiopentone (0.96) was significantly more rapid than the transfer of Midazolam (0.66) and Alpha – hydroxy Midazolam (0.28). elimination half – life in neonates was 6.3 hours for Midazolam and 14.7 hours for Thiopentone.

10. Celleno D. et at (1989) studied the neurobehavioural effects of Propofol on the neonate following elective caesarean section. Forty mothers undergoing elective caesarean section under general anaesthesia were allocated randomly to receive either propofol 2.8 mg kg-1 (n=20) or Thiopentone 5mg kg-1 (n=20). He found that infant in the Propofol group had lower Apgar scores at 1 and 5 min: 25% of them had muscular hypotonus at 5 min. this hypotonus was not noted during the early Neonatal Neurobehavioural scale (ENNS) examination. Newborn children examined 1 h after birth after maternal anaesthesia with Propofol, showed a depression in alert states, pin prick and placing reflexes, and mean decremental count in Moro and light. There was a generalized irritability in 25% of them. This depression was not observed at 4h.

11. Crawford M. E. et al (1989) compared Thiopentone and Midazolam induction in 40 women planned for caesarean section. They found no statistically significant difference in both groups at
and heart rate. Vomiting was significantly more frequent after Thiopental. So Midazolam appears to be suitable alternative to Thiopental for induction and maintenance of anaesthesia.

12. Moore J. et al 1989, compared Propofol and Thiopentone as induction agents in obstetric anaesthesia. They found that blood pressure was lower in the Propofol group during the induction – delivery interval. Umbilical/maternal vein ratios for Thiopentone and Propofol were 8.5 and 7.2 respectively. Infant well being is judged by Apgar score and cord blood analysis showed little difference between the two induction agent. Factors associated with uterine relaxation and bleeding were similar in two groups.

13. Ravlo O. et al (1989) assessed the general condition of 40 neonates following Thiopental or Midazolam based general anaesthesia for elective caesarean section and concluded that Midazolam is as safe as Thiopentone.

14. Valtonen M. et al (1989) compared Propofol and Thiopental for induction of anaesthesia for elective caesarean section. He concluded that induction characteristics and hemodynamic response to Propofol and Thiopentone were similar. Side effects were rare with both agents, but Propofol caused more discomfort on injection compared to Thiopentone. Recovery times were shorter after Propofol as evaluated by time to orientation, recovery scoring after anaesthesia and measurement with the Maddox wing. Rapid placental transfer and significant fetal uptake were detected for Propofol. There was no significant neonatal depression as
assessed by Apgar scores & blood gas analysis. Propofol appears to be a suitable alternative to Thiopentone as an induction agent for anaesthesia in elective caesarean section.

15. Gin T. et al (1990) studied the haemodynamic effects of Propofol and Thiopentone for induction in forty women for elective caesarean section. He concluded that post induction arterial pressures were similar to pre-induction values with no differences between Thiopentone and Propofol. Following intubation, the rise in systolic arterial pressure was greater in the Thiopentone group, 32.1 mm Hg (SD 23.7) compared with the Propofol group, 17.4 mm Hg (SD 23.8), $P<0.05$. In the Thiopentone group, arterial pressures were slower in returning to baseline values. Heart rate initially elevated in both groups to the same degree. At caesarean section, induction with Propofol causes less variation in arterial pressure than Thiopentone. Hypotension is probably prevented by the coincident stimulus of rapid sequence induction. Neonatal Apgar scores were similar between the two groups.

16. Gin T. et al (1990) compared the pharmacokinetics of a bolus induction dose of Propofol 2 mg/kg in 10 women undergoing elective caesarean section with those in six non-pregnant women having laparoscopic sterilization. Non compartmental analysis estimated that the women undergoing caesarean section had a similar elimination half life (mean 81.27 (SD 18.87) min) and apparent volume of distribution at steady state (2.66 (0.63) litre/kg) as non-obstetric patients (99.45 (29.40) min and 3.360 (1.87) litre/kg). Clearance was more rapid in the caesarean section
17. Gin T. et al 1990 studied the maternal and fetal level of Propofol at caesarean section. Twenty women were given a bolus induction of Propofol 2.0mg kg⁻¹ for caesarean section they found that at delivery the maternal venous (MV) concentration of Propofol ranged from 0.53 to 1.48 µg/ml, umbilical vein (UV) 0.39 to 1.4 mg/ml and umbilical artery (UA) 0.34 to 0.68 µg/ml. MV Propofol concentrations were always higher than corresponding UV concentrations. The mean UV/MV ratio was 0.65 (0.56-0.74) and the mean UA/UV ratio was 1.07 (0.99-1.15). Neither ratio was shown to be correlated with induction to delivery time. Distribution of Propofol is rapid across the placenta and in the fetus. Apgar scores higher with shorter incision to delivery times but were not correlated to umbilical level of Propofol.

18. Gregory MA. et al (1990) studied the Propofol infusion anaesthesia for caesarean section. After induction of anaesthesia with Propofol 2 mg/kg, ten pregnant women received Propofol 6 mg/kg/hr and nitrous oxide 50 percent in oxygen while ten were given Propofol 9 mg. Kg⁻¹ hr⁻¹ with 100 percent oxygen. The other ten pregnant women received Thiopentone 4 mg. Kg⁻¹ and nitrous oxide 50 percent in oxygen with enflurane one percent. Haemodynamic changes were similar immediately following induction but the low Propofol infusion group had the best haemodynamic stability subsequently. Recovery times were fastest in the low infusion group but there were no difference in later postbox testing.
Neonatal Apgar scores and umbilical blood gas analysis were similar but NACS at two hours were poorer in the high infusion group. A Propofol infusion coupled with nitrous oxide appears to be a satisfactory technique for Caesarean section.

19. Kanto J. et al (1990) studied the pharmacokinetics and pharmacodynamics of induction agent Propofol in caesarean section. The induction properties and pharmacokinetics of Propofol, 2.5 mg/kg i.v., were studied in twelve unpremedicated healthy pregnant patients at term. The onset of anaesthesia was rapid (27.7 ± 1-7.3 sec) and the quality of induction, maintenance of and rapid recovery from anaesthesia were clinically very acceptable. On the basis of Apgar scores and blood gas analyses of the fetoplacental unit, Propofol appears to be a safe alternative to other available induction agents. The pharmacokinetics of Propofol in pregnant women were described by a high value for total body clearance (mean 2189.6 ml/min) and a short elimination half-life (mean 24.1 min).

20. Gin T. et al (1991) compared the pharmacokinetics of a bolus dose of Propofol 2 mg kg-1 in eight patients undergoing caesarean section with those in eight postpartum patients undergoing sterilization by mini-laparotomy. Caesarean section group had a total body clearance of (medium) 31.5 (range 24.4-6.61) ml min-1 kg-1, apparent volume of distribution at steady state 5.10 (2.46-6.61) litre kg-1 and mean residence time 1.61 (52.3-251) min : volume for postpartum groups were 33.8 (21.5-47.2) ml min-1 kg-1, 5.17 (3.47-8.09) litre kg-1 and 163 (92.3-23.8) min respectively.
Concentration interval for the unbound Propofol in maternal venous ratio of Propofol at delivery was 0.62-0.86 Plasma protein binding studies showed there was less unbound Propofol in maternal plasma (1.28-2.29%) compared with umbilical plasma (2.08-3.88%) (p<0.01). Neonatal concentrations of Propofol were greater than maternal concentrations at 2 hours.

21. Yau G. et al (1991) studied the Propofol for induction and maintenance of anaesthesias at caesarean section in a comparison with Thiopentone/enflurane. Twenty patients received Propofol 2mg/kg for induction of anaesthesia followed by Propofol 6mg/kg/hour, while twenty patients received Thiopentone 4 mg/kg with enflurane 1% for maintenance of anaesthesia. The hypertensive response after intubation was of shorter duration in the Propofol group compared with the Thiopentone group. Induction to delivery times ranged from 5 to 14 minutes and neonates from both groups had similar and satisfactory Apgar scores. Neurologic and Adaptive capacity scores and umbilical cord blood gas analysis. However, a prolonged Propofol infusion time before delivery may cause lower neurologic and adaptive capacity scores. There were no differences in maternal recovery times or psychomotor performance.

22. Siafaka I. it al (1992) compared Propofol and thiopental as induction agents for elective caesarean section. He found that there were no significant differences in haemodynamic response between the two groups, during intubation heart rate rose in both groups, but remained increased five minutes after tracheal intubation only in
monatal depression as assessed by Apgar scores & blood gas analysis. Propofol appears to be a suitable alternative to thiopental as an induction agent for obstetric anaesthesia.

23. Audibert G.B, et al (1993) studied the concentration of Propofol in maternal and fetal blood during anaesthesia for caesarean section. Ten patients were studied in which anaesthesia was induced and maintained with Propofol (2mg/kg in 15 seconds; 3 mg/kg/h until the end of the operation). A series of maternal blood samples have been obtained at delivery. The results (measured by high pressure liquid chromatography) were: at delivery the mean ratio of the drug concentration in the umbilical vein to that in maternal vein was 0.53 ± 0.16 mg/ml: the mean concentration in the umbilical vein was 0.96 ± 0.31 mg/ml. The anaesthesiological protocol was clinically satisfactory and had no adverse effects on mother and foetus.

24. Celleno D, et al (1993) compared the thiopental sodium, Propofol and midazolam for induction of anaesthesias in patients undergoing elective caesarean section. Three groups of 30 patient each receiving thiopental 5 mg/kg, Propofol 2.4 mg/kg or midazolam 0.3 mg/kg for induction of anaesthesia. He found that in the thiopental and midazolam groups, systolic blood pressure and heart rate rise following endotracheal intubation and skin incision (p < 0.001 and p < 0.0025, respectively), while in the Propofol group, there was significant hypotension after induction (p < 0.005) electroencephalographic patterns showed a light depth of
anaesthesia with Propofol and midazolam between anaesthesia induction and delivery, confirmed by the presence of clinical signs of light anaesthesia in 50% of Propofol patients and 43% of midazolam patients. Time to induce anaesthesia was longer with midazolam (p < 0.00001). Neonates in the midazolam and Propofol groups had lower Apgar and neurobehavioural scores than those in the thiopental group. Umbilical artery to umbilical vein ratio were above 1 in the Propofol and midazolam groups.

25. Gin T, et al (1993) studied the plasma catecholamines and neonatal condition after induction of anaesthesia with Propofol or Thiopentone at caesarean section. They found that the increase from baseline values in mean arterial pressure after tracheal intubation was greater in the Thiopentone group [29 (SD 15) mm Hg] compared with the Propofol group [18 (14) mm Hg] (p < 0.01). The concentrations of noradrenaline and adrenaline increased in both group after tracheal intubation. Maximum noradrenaline concentration were greater in the Thiopentone group [413(177) pg/ml] compared with the Propofol group [333(108) pg/ml] (P< 0.05), but there were no differences between groups in adrenaline concentrations. Neonatal Apgar scores, neurobehavioural testing and umbilical catecholamine, blood gas tension and oxygen content analysis were similar between groups. Propofol attenuated the hypertensive and catecholamine response associated with laryngoscopy and tracheal intubation but there was no improvement in neonatal outcome.
26. Sariev A.K. et al (1993) studied the pharmacokinetics and pharmacodynamics of thiopental sodium in pregnant women during caesarean section. Group I consisted of 6 women (Thiopental dose 8.0 mg/kg was combined with components of neuroleptanalgesia), group II consisted of 7 women (The drug dose 4.68 mg/kg was combined with moradol analgesia). The higher Apgar score was characteristic of the newborns from group II due to the potentiating effect of moradol. In both groups a correlation has been established between pharmacokinetic parameter and haemodynamic changes, as well as between sodium thiopental concentration in maternal and umbilical blood and pharmacokinetic parameters.

27. Teviotdale B.M. et al (1993) studied the Vecuronium-Thiopentone induction for emergency caesarean section under general anaesthesia. In this series of thirty cases vecuronium 8 mg preceding Thiopentone 250mg and atropine 0.6mg by 20 seconds provided effective induction and easy intubating conditions without clinical effects on the newborn maternal acid aspiration, or clinical signs of persistent paralysis after reversal.

28. Zamora E. et al (1994) studied the effects on the newborn infant of thiopental and Propofol used in anaesthetic induction in caesarean section. Anaesthesia was induced with thiopental 4 mg/kg in one group; in the other group, Propofol 2mg/kg was used. He concluded that if the induction extraction interval is 10 min or less, both thiopental (4 mg/kg) and Propofol (2 mg/kg) given in a single
section are equally safe for the new born infant.

29. Kee W.D. et al (1997) studied the post operative analgesic requirement after caesarean section: a comparison of anaesthetic induction with ketamine or thiopental. He compared postoperative pain and analgesic requirement in patients who underwent elective caesarean section under general anaesthesia induced with thiopental 4mg/kg or ketamine 1mg/kg. Anaesthesia was maintained with nitrous oxide and isoflurane. Post operative analgesia was provided by Patient Control Analgesia (PCA) using morphine. He concluded that induction of anaesthesia for caesarean section using ketamine is associated with a lower postoperative analgesic requirement compared with thiopental. Ketamine unlike thiopental has analgesic properties that may reduce sensitisation of pain pathways and extend in to the postoperative period.

30. Djordjevic B. et al (1998) compared propofol and Thiopentone as induction agent for elective caesarean section. A total of 40 female patients were randomly divided in two equal groups each of them was to receive different anaesthetic: Propofol 2.5 mg/kg (n=20) or Thiopentone 5mg/kg (n=20. they concluded that following induction of anaesthesia a significantly greater decrease of blood pressure and heart rate was found in the Propofol group, when compared with the patients in Thiopentone group. During the induction and maintenance of anaesthesia, the frequency of adverse effects was greater in Thiopentone, than in Propofol group (6/20 versus 2/20 patient). There was no significant difference between
new-borns from the propofol group had significantly higher Apgar score in the 1st minute (8.35) and 5th minutes (9.25), than the new-borns in Thiopentone group (7.90) and 8.90, respectively.

31. Sanchez-Alcaraz A. et al 1998 studied the Placental transfer and neonatal effect of Propofol in caesarean section. Intravenous Propofol was administered as an anaesthesia — inducing agent at doses of 2 mg kg-1 in ten healthy pregnant women (ASA I-II). They concluded that Propofol plasma levels in the newborn at the time of delivery depend on the level in maternal plasma, and therefore on the dose used for induction and the time lapsed between the administration of the drug and the delivery of the foetus.

32. Kotur P.F. et al (2000) compared the injection Propofol and injection Thiopentone as induction agents in anaesthesia for caesarean section. He resulted that induction characteristics were comparable in both groups. Induction time and time for recovery were faster in Propofol group when compared with Thiopentone group. There were clinically acceptable haemodynamic changes in both groups and Apgar scores at 1 mm and 5 min were comparable between two groups. Incidence of complications were nil in both groups except involuntary muscle movement in five patients during induction in Propofol group.