Thiopentone Sodium

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Name: Sodium thiopental, better known as Sodium Pentothal, thiopental, thiopentone sodium
Class: Ultra short acting barbiturates.

Structure:

1. IUPAC name: (RS)-[5-ethyl-4,6-dioxo-5-(pentan-2-yl)-1,4,5,6-tetrahydropyrimidin-2-yl] sulfanide sodium
2. Sodium 5- ethyl, 5- (1- methyl butyl),2-thiobarbiturate
3. It is a sulphur analogue of sodium pentobarbital.

Commercial Preparations:

1. The S (-) isomers are twice as potent as R (+) isomers, but commercially available as racemic mixture.
2. Commercially available sodium thiopentone is a pale yellow, hygroscopic amorphous powder with a smell of hydrogen sulphide. The powder contains mixture of 6 parts anhydrous sodium carbonate as buffer (60 mg/g of thiopental sodium) to prevent precipitation of the insoluble acid form of barbiturate by atmospheric carbon dioxide.
3. For the above reason, it is prepared in atmosphere of nitrogen.
4. Yellow colour is due to the presence of sulphur molecule.
5. The powder is soluble in distilled water, normal saline and alcohol.
6. It should be reconstituted in distilled water or normal saline to prevent precipitation. (Avoid Lactated Ringer’s solution). It should be prepared as 2.5% solution as higher concentrated solution will result in higher pH (more alkaline solution).
7. Solution of 2.5% in distilled water is isotonic.
8. pH of 2.5% solution is 10.5 which is highly alkaline, so it has optimal aqueous solubility at high pH values. At physiological pH where drug is in slightly more than half unionized state, it can precipitate from solution. It is a weak acid of pKa = 7.60.
9. These highly alkaline solutions are incompatible for mixture with drugs in acidic solutions such as opioids, catecholamines, neuromuscular blocking drugs.
10. The bacteriostatic properties of commercial preparations are due to their highly alkaline pH. It does not contain antibacterial agents.

11. The powder form is stable at room temperature indefinitely. The reconstituted solution (2.5%) is stable and sterile for 6 days at room temperature (22°C) and for 2 weeks at 4-8°C.

12. Cloudy solution should be discarded.

History:

1. It was synthesized in the early 1930s by Ernest H Volwiler and Donalee L. Tabern, working for Abbott Laboratories.

2. It was first used in human beings on March 8, 1934, by Dr. Ralph M. Waters in an investigation of its properties, which were short-term anaesthesia and surprisingly little analgesia.

3. Three months later, Dr. John S. Lundy started a clinical trial of thiopental at the Mayo Clinic at the request of Abbott Laboratories.

4. Thiopental is (in) famously associated with a number of anaesthetic deaths in victims of the attack on Pearl Harbor during the World War II (7th December 1941). These deaths were due to cardiovascular depression as excessive doses (used as sole anaesthetic agent) were given to hypovolemic shock patients. After this incidence, its use declined for sometimes. After a series of investigations, it was concluded that improper use of thiopentone rather than the drug itself was responsible for death. (Ref: Bennetts FE. Thiopentone anaesthesia at Pearl Harbor. BJA 1995; 75:366-368.)
Mechanism of action:

Ultra short-acting barbiturate anaesthetics depress the central nervous system (CNS) to produce hypnosis and anaesthesia without analgesia. The exact mechanism by which barbiturate anaesthetics produce general anaesthesia is not completely understood, but multiple site action has been observed:

1. **Site of action:** GABA: BZD: Chloride receptor complex in CNS

   When GABA_A receptors are activated, trans-membrane chloride conductance increases, resulting in hyperpolarisation of post-synaptic cell membrane and functional inhibition of post synaptic neurons.
   - Thiopentone reduces dissociation of GABA from these receptors (GABA facilitatory action).
   - It also mimics action of GABA by directly activating GABA_A receptors.

2. It also acts on glutamate receptors, adenosine receptors, and neuronal nicotinic acetylcholine (nAChR) receptors.

3. Directly depressing excitability by increasing membrane conductance (an effect reversed by the GABA antagonist picrotoxin), thereby producing a net decrease in neuronal excitability to provide anaesthetic action.

4. Inhibit Ca^{2+} dependent release of neurotransmitter.

   - Selective depresses transmission in sympathetic nervous ganglia to produce hypotension at sub-hypnotic dose.
   - At NM junction, decreases sensitivity of post synaptic membrane to the depolarising action of Ach.

Pharmacokinetics:

1. **Molecular weight** — 264.33
2. **pKa** — 7.4
3. Oil: water partition coefficient — 580
4. **Absorption:** gastro-intestinal: Thiopental rectal suspension — May be unpredictable
   **Intravenous:** Predictable.
5. **Volume of distribution at steady-state (Vd):** 1.7 to 2.5 L/kg; may increase to 4.1 L/kg during pregnancy at term and to 7.9 L/kg in obese patients.
6. **Protein binding:** — Protein binding parallels to lipid solubility (i.e. unionized component). Thiopentone is a highly lipid soluble drug with high protein binding, with
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binding to albumin ranging from 72 to 86%. Decreased protein binding due to hypoproteinemia (cirrhosis of liver) or due to competitive displacement by nitrogenous waste products in uraemia or aspirin, phenylbutazone may lead to increased free fraction of the drug; hence enhanced effect.

7. **Distribution: Three compartment phase model after intravenous injection**
   - **Alpha-1 phase**: (1.7 - 6.5 minutes): Distribution Half life
     Because of their high lipid solubility and low degree of ionization at physiological pH, barbiturate anaesthetics rapidly distributes to highly perfused organs like brain, heart, liver, kidney. Since pKa of thiopentone (7.6) is near blood pH, acidosis will favour the non-ionised fraction of drug, whereas alkalosis will favour ionised fraction of drug. Non-ionised fraction is more lipid soluble and will have greater CNS penetration.
   - **Alpha-2 phase**: (23 - 71 minutes)
     Drugs are rapidly redistributed from the brain/other highly perfused area to other body tissues first to muscle, and then slowly to fat.

     With a fat: blood partition coefficient of 11, thiopental will move from blood to fat as long as the concentration in the fat is less than 11 times that in blood. Maximal deposition in fat is present after about 2.5 hours, and fat becomes potential reservoir of drug particularly large boluses/infusion has been given. It may result in prolonged anaesthesia, somnolence, and respiratory and circulatory depression
   - **Beta phase**: (206 - 1321 minutes)- Elimination by metabolism begins after 15 minutes of drug administration.

8. **Metabolism**
   - Thiopentone is almost completely metabolised before excretion, less than 1% of unchanged drug is present in urine.
   - Primary site of metabolism is liver; small extent in other tissues, especially the kidneys and brain.
   - Thiopentone is metabolised by oxidation of substitutes at 5’ C, desulfuration on 2’ C and hydrolytic opening of ring chain into hydroxylthiopental and carboxylic acid derivatives, which are more water soluble with little CNS activity. Although most of thiopental's metabolites are inactive, about 3 to 5% of a dose is desulfurated to pentobarbital, which is cleared from the body much more slowly than thiopental. The
significance of this metabolic pathway is relevant only in patients receiving large
doses of thiopental.

- Hepatic clearance of thiopentone has low hepatic extraction ration and capacity
dependent elimination influenced by hepatic enzymes but not hepatic blood flow. So,
when large quantities of thiopental are administered by continuous intravenous
infusion over a prolonged period of time, progressively increasing saturation of
hepatic metabolizing enzymes may occur, resulting in a rapid increase in the plasma
contentration. Also, enzyme induction may lead to increased metabolism.

- All the inactive metabolites are excreted through kidney.
- Clearance: 3.4 ml/kg/minutes
- Elimination half life:
  - Adults—3 to 8 hours after a single intravenous dose;
  - Children—6.1 hours
  - The elimination half-life may be longer after prolonged administration (10
to 12 hours)
  - The elimination half-life increases with increasing age and is dependent
    on hepatic blood flow
  - It may be increased to 26.1 hours during pregnancy at term and to 27.85
    hours in obese patients.

  Note: When low doses of thiopental (e.g., 5 mg per kg of body weight)
are administered for induction of anaesthesia, the elimination half-life is
independent of plasma concentration (first order kinetics).
Administration of high doses of thiopental (e.g., 300 to 600 mg per kg of
body weight) results in an increase in the elimination half-life (zero order
kinetics).

9. **Onset of action:** Rapid, due to the high lipid solubility of the barbiturate
anaesthetics.

  - Anaesthesia:
    - Intravenous—30 to 40 seconds
    - Rectal—Within 8 to 10 minutes.

  **Note:** Following intravenous administration of induction doses of thiopental,
muscle relaxation occurs about 30 seconds after unconsciousness is
attained. After intravenous administration of induction doses of a barbiturate
anaesthetic, the depth of anaesthesia may increase for up to 40 seconds and
then decrease progressively until consciousness returns. This reflects rapid
changes in the concentration of the anaesthetic at its sites of action in the
brain and is a consequence of its initial distribution to the brain followed by subsequent redistribution to other tissues.

- Hypnosis: Intravenous—Within 10 to 40 seconds

10. Time to peak concentration:

Intravenous administration: Brain: within 30 seconds, Muscles: 15 to 30 minutes. Fat: Several hours

Note: Very highly perfused tissues such as the brain, heart, liver, and kidneys achieve concentrations equal to peak plasma concentrations.

11. Duration of action: Intravenous administration: 10 to 30 minutes.

Note: The brief duration of action is due to the rapid rate of redistribution and, to some extent, metabolism accompanied by a rapid fall in plasma concentration. Administration of large or repeated doses may substantially delay recovery.

Uses

1. Induction of general Anaesthesia:
   a. 3-5mg/kg body weight (dose varies with age, weight and cardiac output).
   b. Onset of action: 10-30 sec
   c. The dose should be calculated according to the lean body weight to avoid overdose.

2. Maintenance of General anaesthesia (along with opioid):
   a. Barbiturate anaesthetics may be administered in appropriate doses and in combination with an opioid analgesic and nitrous oxide for maintenance of anaesthesia in prolonged procedures, but not used these days.
   b. 50-100 mg every 10-12 minutes, chance of accumulation and hence delayed awakening.

3. Pre-anaesthetic Sedation: Rectal suspension may be used, although absorption from the rectum is unpredictable.

4. Sedation: The barbiturate anaesthetics are used sometimes for sedation during short surgical operations, diagnostic procedures, or regional anaesthesia in adults. Rectal thiopental often is used as the sole sedative/induction agent for diagnostic procedures (e.g., computerized axial tomography [CAT] scans or magnetic resonance imaging [MRI]) in children.
5. **Convulsions (treatment)**—Thiopental for injection (3mg/kg) is indicated for short-term use in the control of convulsive (GTCS) states during or following inhalation anaesthesia, local anaesthesia, or other causes.

6. **Treatment of increased Intracranial Pressure**: 3mg/kg body weight. Thiopental for injection may be indicated in the treatment of increased intracranial pressure if adequate ventilation is provided. It may be used to attenuate the increase in intracranial pressure during the use of volatile anaesthetics. It also may be useful in the management of conditions associated with acutely increased intracranial pressure, such as Reye's syndrome, cerebral edema, and acute head injury.

7. **Narcoanalysis**: Thiopental for injection is indicated for narcoanalysis in psychiatric disorders.

8. **Cerebral protection**: Thiopental for injection is indicated to protect the brain from the effects of hypoxia and ischemia following head injuries and other related conditions.

**Contraindications:**

**Absolute contraindications:**

1. Acute intermittent porphyria (thiopentone induces mitochondrial enzyme D-aminolevulinic acid synthetase. As a result, production of heme is accelerated, and acute intermittent porphyria may be precipitated in susceptible patients)
2. Barbiturate allergy
3. H/O paradoxic excitation
4. Status asthmaticus: In severe asthma it is thought that thiopentone may occasionally cause bronchospasm.

**Relative contraindications:**

1. Patients with a low circulating blood volume, such as after haemorrhage, are prone to severe hypotension with thiopentone. (barbiturate anaesthetics produce cardiovascular depressant effects; condition may be exacerbated)
2. Patients with cardiac disease (particularly those with stenotic heart valve lesions) are at risk from the cardiovascular depressant effects of thiopentone. The drug must be carefully titrated against effect.
3. Patients with partial airway obstruction, acute inflammation of mouth/ upper airway should not be given an intravenous anaesthetic agent as total airway obstruction develops.
4. Hepatic dysfunction
5. Uraemia/ renal insufficiency (hypnotic effect may be prolonged or potentiated)
6. Uncontrolled Diabetes/ Adrenal cortical insufficiency/ mexedema
7. Hypokalemic familial periodic paralysis
8. Dystrophia myotonica, Myaesthenia Gravis, Huntington’s chorea (respiratory depression may be prolonged; dosage should be carefully titrated)
9. Thermally injured children (hypotension, require large dose 7—8 mg/kg
10. Children less than 1 year of age: respiratory centre easily depressed, relatively large dose required.
11. Alcoholic patient taking disulfiram

**Advantages:**
1. Pleasant, smooth, rapid induction
2. Smooth and rapid recovery.
3. Absence of stage of delirium
4. Depth of anaesthesia can be increased rapidly.

**Disadvantages:**
1. CVS and Respiratory depression
2. No loss of cough reflex and laryngeal reflex: Coughing, laryngospasm
3. Local and systemic reactions
4. Poor muscular relaxation

**Pharmacodynamics:**
1. Central Nervous System
   a. Dose dependent depression of cerebral cortex, ascending reticular activating system and medullary centre resulting in sedation, hypnosis, anaesthesia, respiratory depression.
   b. Decrease in Cerebral metabolic oxygen consumption, Cerebral blood flow and ICP
   c. Anticonvulsant effect
   d. Stimulates CTZ, so nausea and vomiting
   e. It has no analgesic property. Ant-analgesic property has not been verified.
2. Cardiovascular System:
   a. Myocardial depression: dose dependent
   b. Mean BP: There is either a fall in or no change in mean arterial blood pressure depending on volume status.
   c. Compensatory increase in heart rate due to decrease in mean BP
d. Cardiac Output: Decreases, more significant in hypovolemic patients, cardiac
disease, on beta blockers, hypertensive patients on treatment

e. an increase in total calculated peripheral resistance; an increase or no
change in heart rate; a considerable decrease in renal plasma flow; a
decrease in intra-thoracic blood volume; an increase in blood flow and volume
in the extremities; a decrease or no change in the central, right atrial, and
peripheral venous pressures; and a decrease in cerebral blood flow with a
marked reduction in cerebrospinal fluid (CSF) pressure. Direct depression of
cardiac contractility is dose-related.

3. Respiratory System:
   a. Dose dependent respiratory depression (first depth then rate)
   b. Decreased sensitivity of respiratory centre to increase in carbon dioxide.
   c. Apnoea may be present in 30-40% cases.
   d. Laryngeal reflexes and cough reflexes are not depressed until large doses
      are given.
      During induction of anaesthesia or in lightly anesthetized patients,
laryngospasm and bronchospasm may be induced by a variety of stimuli such
as surgical stimulation, the premature insertion of the laryngoscope blade or
airway, and pharyngeal secretions. Laryngospasm and airway obstruction can
occur with any route of administration of barbiturate anaesthetic.

4. Liver:
   a. Blood flow is not affected (rather increases hepatic blood flow) unless there is
      hypoxia.
   b. Induction of microsomal enzymes

5. Kidney:
   a. Constriction of splanchnic and renal blood vessels: decrease in RBF and
      GFR.

6. GIT: Decrease in peristalsis.

7. NM Junction:
   a. Minimal muscle relaxation
   b. Localised muscle spasm (pronation of forearm receiving the injection which
      can be decreased by narcotics)

8. Eye:
   a. Pupil first dilate and then constrict
   b. Sensitivity to light remains until the patients is deep enough to permit skin
      incision. At this stage, eyeballs are centrally placed.
c. Decrease in IOP.
d. Loss of eyelash reflex is the sign of induction of anaesthesia.

9. Pregnant Uterus:
   a. Barbiturate anaesthetics have no effect on uterine muscle tone.
   b. Crosses placenta (equilibrium between mother and foetus within 2-3 minutes)

**Precautions to Consider:**

1. **Cross-sensitivity and/or related problems:** Patients sensitive to one barbiturate may be sensitive to other barbiturates also.

2. **Carcinogenicity/Mutagenicity:** Studies in animals have not been performed to determine the carcinogenic and mutagenic potential of thiopental.

3. **Fertility:** Studies in animals have not been performed to determine the effect of thiopental on fertility.

4. **Pregnancy:** Use of barbiturate anaesthetics during pregnancy may cause CNS depression in the foetus. Adequate and well-controlled studies in humans have not been done to determine whether barbiturate anaesthetics are teratogenic. *Thiopental crosses the placenta.* The concentration in cord vein blood is at its maximum 2 to 3 minutes after an intravenous dose is administered to the mother. FDA Pregnancy Category C.

5. **Breast-feeding:** Problems in humans have not been documented. However, barbiturate anaesthetics are distributed into breast milk; small amounts may appear in breast milk following administration of large doses to the nursing mother.

6. **Paediatrics:** Infants and children require slightly more thiopental on a weight basis than adults require. Respiratory centres are easily depressed. Thiopental is not labelled by the FDA for intravenous administration to paediatric patients.

7. **Geriatrics:** Following administration of barbiturate anaesthetics for short (outpatient) procedures, recovery of cognitive and psychomotor functions is generally slower in elderly patients than in younger adults. In addition, elderly patients are more likely to have age-related hepatic function impairment, which may require reduction of dosage in patients receiving barbiturate anaesthetics, and age-related renal function impairment, which may prolong the effects of these medications.

8. **Obese patients:** Calculate dose according to lean body mass. Decreased dose is required. There may be prolonged effect due to accumulation of drug in fat.
Side/Adverse Effects

Local:

1. On intravenous/ perivenous injection, it may cause pain, swelling, ulceration, hematoma due to its high pH (highly alkaline). Treatment is 10ml of 1% xylocaine with hydralase 1000U into area (causes vasodilatation and absorption of drug).

2. Accidental intra- arterial injection:
   a. In 10% cases, division of brachial artery occurs above elbow. The abnormal ulnar artery is in superficial position immediately deep to median cubital vein and without protection of aponeuritic tendon of biceps. It may be accidently punctured and may be used for injection of drugs. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel.
   b. The pH of 2.5% drug solution is 10.5 (strong alkali). When it is injected into artery and mixed with blood (pH= 7.4= less alkaline) it gets precipitated as solid crystals of thiopentone and haemoglobin. It results in local inflammation and blocks small arterioles, causes vasospasm due to local release of noradrenaline.
   c. Accidental intra-arterial injection can cause arteriospasm and severe pain along the course of the artery with blanching of the arm and fingers. Later on, oedema, ulceration and gangrene of hand/ arm may follow. Onset of unconsciousness is delayed.
   d. Appropriate corrective measures should be instituted promptly to avoid possible development of gangrene. Any patient complaint of pain warrants stopping the injection. Methods suggested for dealing with this complication vary with the severity of symptoms. The following have been suggested:
      i. Leave the needle in place (do not take out needle otherwise we may lose artery access).
      ii. Inject 500U heparin (it reverses alkalinity and prevents thrombosis).
      iii. Inject 5 ml xylocaine 1- 2% into the artery.
      iv. Dilute the injected Pentothal (Thiopental Sodium for Injection, USP) by removing the tourniquet and any restrictive garments and flush with normal saline.
      v. Inject the artery with a dilute solution (10- 20ml) of papaverine, 40 to 80 mg, or 10 mL of 1% procaine, to inhibit smooth muscle spasm.
vi. Continue anaesthesia with Halothane (vasodilator)

vii. Postpone surgery if possible.

viii. Oral anticoagulants may be required.

ix. If necessary, perform sympathetic block of the brachial plexus and/or stellate ganglion to relieve pain and assist in opening collateral circulation.

x. Papaverine can be injected into the subclavian artery, if desired.

xi. Consider local infiltration of an alpha-adrenergic blocking agent such as phentolamine into the vasospastic area.

xii. Provide additional symptomatic treatment as required.

3. Thrombophlebitis: less chance with 2.5% solution. It is also due to precipitation of crystals.

General:

1. CNS: post-operative vertigo, anxiety or restlessness seizures, euphoria, disorientation,
   a. Excitatory phenomena such as involuntary muscle movements, coughing, and hiccups
   b. Emergence delirium (anxiety; confusion; excitement; hallucinations; nervousness; restlessness)

2. CVS: circulatory depression, hypotension, tachycardia, cardiac arrhythmias

3. Respiratory: Respiratory depression, bronchospasm, laryngospasm, coughing, wheezing

4. GI: Abdominal pain, hiccups, nausea or vomiting
   a. With rectal administration only: Burning, cramping, diarrhoea, rectal irritation

5. muscle twitching or jerking — occurring during induction of anaesthesia or in light anaesthesia

6. Increased sensitivity to cold, during recovery (shivering or trembling)

7. Allergy (anaphylaxis): skin rash, hives, itching, or redness, swelling of eyelids, face, or lips

8. Immune haemolytic anaemia with renal failure (back, leg, or stomach pain; nausea, vomiting, or loss of appetite; unusual tiredness or weakness; fever; pale skin

9. Immuno-suppression

10. Tolerance and physical dependence

11. Overdose can result from too rapid or repeated injections of barbiturate anaesthetics
Acute effects: CNS depression, severe, hypotension, severe loss of peripheral vascular resistance, respiratory depression, severe, including apnoea

Treatment of overdose: Discontinuation of the anaesthetic.
Specific treatment—If over-dosage occurs with a rectal barbiturate anaesthetic preparation, the contents of the rectum should be promptly evacuated; further dosing should be delayed until the effects of absorption of the initial dose can be determined.

Monitoring—Vital signs, blood gases, and serum electrolytes should be monitored.
Supportive care—Supportive measures such as establishing and maintaining a patent airway (by endotracheal intubation if necessary), administering 100% oxygen with assisted ventilation if necessary. For hypotension—Intravenous fluids should be administered and the patient's legs raised. If a desirable increase in blood pressure is not obtained, vasopressor and/or inotropic drugs may be used as required.

Drug interactions and/or related problems:

1. Alcohol or other CNS depressant- pre-anaesthetic medication or induction or supplementation of anaesthesia- concurrent administration may result in increasing the CNS depressant, respiratory depressant, or hypotensive effects of barbiturate anaesthetics as well as decreasing anaesthetic requirements and prolonging recovery from anaesthesia; dosage adjustments may be required.

2. Antihypertensives, especially diazoxide or ganglionic blockers such as guanadrel, guanethidine, mecamylamine, or trimethaphan or Diuretics or Hypotension-producing medications: concurrent use of these medications with barbiturate anaesthetics may result in an additive hypotensive effect, which could be severe; dosage adjustments may be necessary; patients should be monitored for excessive fall in blood pressure during and following concurrent use.

3. Concurrent use of antihypertensives with CNS depressant effects, such as clonidine, guanabenz, methyldopa, metyrosine, pargyline, and rauwolfia alkaloids, may increase the CNS depressant effects of barbiturate anaesthetics.

4. Hypothermia-producing medications: concurrent use with barbiturate anaesthetics may increase the risk of hypothermia.

5. Ketamine (concurrent use of ketamine, especially in high doses or when rapidly administered, with barbiturate anesthetics may increase the risk of hypotension and/or respiratory depression; also, the hypnotic effect of thiopental may be antagonized by ketamine.
6. Magnesium sulfate, parenteral: Concurrent use may increase the CNS depressant effects of barbiturate anaesthetics.
7. Phenobarbital or Phenytoin: (a higher dose of methohexital may be needed.
8. Phenothiazines, especially promethazine (in addition to possibly increasing CNS depressant effects, concurrent use may potentiate the hypotensive and CNS excitatory effects of barbiturate anaesthetics.
9. These highly alkaline solutions are incompatible for mixture with drugs in acidic solutions such as opioids, catecholamines, neuromuscular blocking drugs.