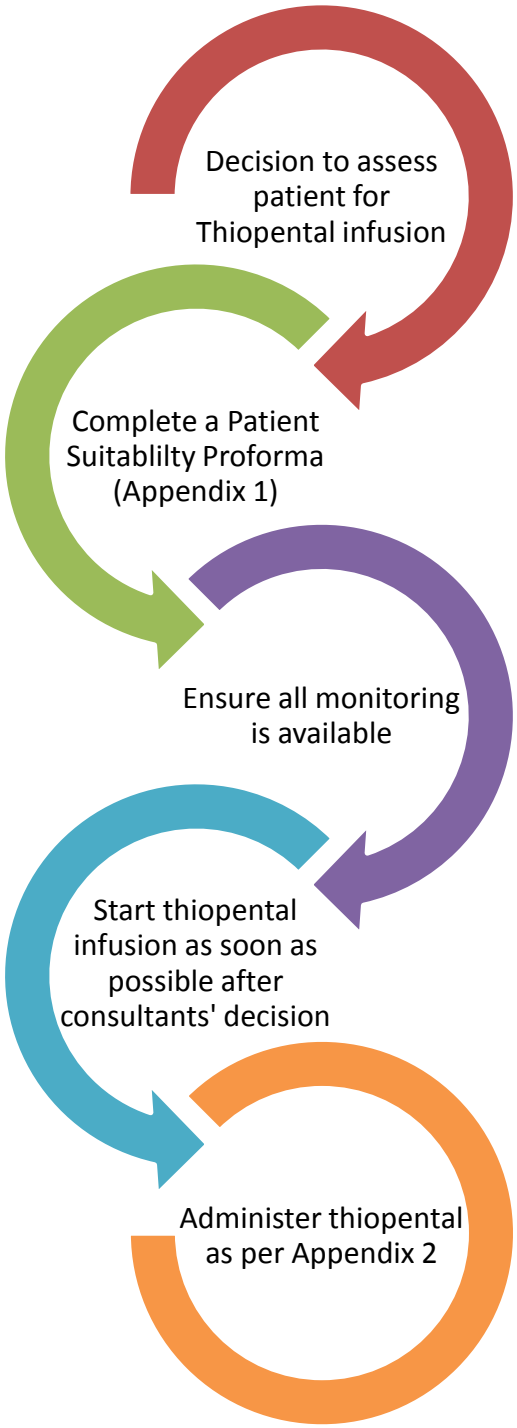
Thiopental Sodium: Use in Patients with Severe Traumatic Brain Injury with Refractory Raised Intracranial Pressure in Critical Care

Thiopental is at Consultant Intensivist and Consultant Neurosurgeon Request Only



Patient has severe TBI with raised ICP unresponsive to primary and secondary management measures (as per BSUH Guidelines for the Management of TBI)

Suitability proforma prompts consideration of primary and secondary measures for managing ICP

EEG or BIS
ICP
Arterial BP monitoring
ECG
Serum K^+
PiCCO if high dose noradrenaline / multiple inotropes

If there is a prolonged delay (more than 24 hours) the patient must be reassessed for suitability and the outcome agreed by the Consultant Intensivist and

Titrate infusion using EEG or BIS
Only consider sending Thiopental levels if concerns over prolonged sedation after infusion discontinued

Background

Barbiturates reduce cerebral metabolism**,** thereby reducing cerebral metabolic demands and cerebral blood volume. They can also reduce blood pressure and may, therefore, adversely affect cerebral perfusion pressure.

High dose thiopental sodium infusions have been used in the treatment of severe head injury complicated by uncontrollable raised intracranial pressure, refractory status epilepticus and acute brain insults associated with cerebral ischaemia.[1]

A continuous infusion of thiopental induces EEG burst suppression.

The Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury state that high dose barbiturate administration is **recommended** to **control** elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.[2]

Administration of barbiturates to induce burst suppression as **prophylaxis** against the development of intracranial hypertension is **not recommended**.[3]

The most recent Cochrane review states that there is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one in four patients. The hypotensive effect will offset any ICP lowering effect on cerebral perfusion pressure.[3]

Indication

High dose thiopental can be used to reduce refractory raised intracranial pressure in patients with severe head injury who are **unresponsive to primary and secondary management measures** as detailed in BSUH Guidelines for the Management of Traumatic Brain Injury**.**

If the patient has a definite history of an episode of severe hypoxia, consider the appropriateness of commencing a high dose thiopental infusion.

Treatment with high dose thiopental therapy will have a prolonged effect, and will delay the time before brain stem tests can be performed.

Before commencing a thiopental infusion complete a Patient Suitability Proforma to ensure primary and secondary management measures have been considered (see Appendix 1). Start thiopental infusion as soon as possible after the Consultants' decision. If there is a prolonged delay of more than 24 hours the patient must be reassessed for suitability and the outcome agreed by the Consultants.

Goals

1. To maintain ICP < 25mmHg
2. To achieve therapeutic EEG response (burst suppression) or BIS value of 10-20 and SR of 60-80%

Contra-indications [4]

Hypersensitivity to barbiturates, respiratory obstruction, acute asthma, severe shock, myotonic dystrophy and porphyria.

Cautions [4]

Cardiorespiratory depression:

Thiopental causes respiratory depression and a reduction in cardiac output and may precipitate acute circulatory failure in patients with cardiovascular disease, particularly constrictive pericarditis. Care should also be exercised with severe cardiovascular diseases, severe respiratory diseases and hypertension.

Particular caution required:

Hypovolaemia, severe haemorrhage, burns, cardiovascular disease, myasthenia gravis, adrenocortical insufficiency (even when controlled by steroids), cachexia, raised blood urea.

Dose reduction required:

Reduced doses are recommended in the elderly, shock, dehydration, severe anaemia, hyperkalaemia, toxaemia, metabolic disorders e.g. thyrotoxicosis, myxoedema, diabetes, renal and hepatic impairment.

Increased doses:

Increased doses may be necessary in patients who are addicted to or regularly use alcohol or drugs of abuse.

Adverse effects [4]

Anaphylactic, hypersensitivity and allergic reactions (rare)
Hypotension, arrhythmias and myocardial depression (common)
Respiratory depression, bronchospasm and laryngospasm (common)
Extravasation – thiopental has a high pH and will cause local tissue necrosis and severe pain if extravasation occurs. Administer via a central venous access device.

Interactions [4]

Enhanced hypotension when thiopental used with any other agent which lowers blood pressure.
Synergistic effects when thiopental used with other CNS and respiratory depressant drugs.

Monitoring

1. **EEG monitoring:** The cortex may be near-silent. However, this does not necessarily mean that sub-cortical activity is also suppressed. An isoelectric EEG can readily be produced and probably represents the best reduction in metabolic demands by the cortex. However, this does not allow titration of thiopental dose and often encourages unnecessarily prolonged use of high infusion rates of thiopental. It is therefore more efficient to ensure that there is

a residual amount of electrical activity in the form of burst-suppression. Burst suppression is characterised by bursts of slow activity (theta and/or delta waves) and/or spikes or sharp waves, with relatively long intervening periods of very low voltage activity.[5] Both can last from 1.5 – 6 seconds.
There is no benefit to monitoring the EEG for subclinical status epilepticus in patients receiving thiopental infusions if burst suppression has been achieved.
BIS (Bispectral index) monitoring is an alternative to EEG monitoring: The bispectral index value and the suppression ratio values have shown to correlate well with the standard EEG based method to titrate barbiturate therapy. **Aim for BIS values of 10-20 and SR values of 60-80%.** This has been shown to correspond to 3-5 bursts per minute on EEG.[6]

2. **ICP monitor**
3. **Arterial blood pressure**
4. **ECG monitoring and plasma K^+:** Refractory hypokalaemia has been reported in patients receiving thiopental infusions. The fall in serum K^+ is thought to be due to metabolic changes within the brain.[7] There is potential for severe rebound hyperkalaemia when the thiopental infusion is ceased. Supplement potassium cautiously, if ECG changes indicate need.
5. **PiCCO monitoring:** if noradrenaline dose > 0.2microgram/kg/min or more than one inotrope required.

Administration: see Appendix 2

Pharmacokinetics
Following a single IV bolus thiopental will be effectively removed from plasma after 5 half-lives. Thiopental demonstrates zero order pharmacokinetics after repeated doses or continuous infusion, due to saturable hepatic metabolism. This means that the **elimination half-life becomes longer as the level of thiopental in the body increases**.
After the infusion has stopped thiopental will be slowly released from fatty tissues causing prolonged anaesthesia, somnolence, respiratory and circulatory depression.

High-dose IV thiopental aimed at achieving burst suppression is **very likely** to result in a **prolonged duration** of clinical effect including **loss of pupillary and motor responsiveness**.[1]

This may pose an ethical dilemma if a decision to modify or withdraw treatment is required when a patient's neurological status may still be influenced by the drug.

Onset of action: After bolus IV administration thiopental acts within one minute.[8]
Duration of action: The effects of a single IV bolus of thiopental last for 5 – 15 minutes. The effect is cumulative after repeated administration. [8]
Metabolism: occurs in the liver: 15% of the dose of the drug is metabolised per hour; 30% may remain in the body 24 hours after bolus administration.[8]
Excretion: occurs predominantly in the urine as inactive metabolites.
Elimination half-life is 3.4 – 22 hours.[8]

Therapeutic Drug Monitoring

A single blood level does not have any clinical significance, but serial levels may help to differentiate causes of prolonged sedation, especially after the infusion has been discontinued.

In most patients with acute and severe brain insults:
Pupillary response may be absent with a serum thiopental concentration >50mg/L [1]
Motor response may be absent with a serum thiopental concentration >12mg/L [1]

Thiopental levels are assayed at Cardiff Toxicology Laboratories Monday-Friday 0900-1700 only. To make arrangements for the assay, please discuss with the BSUH Biochemistry dept and refer to the Cardiff website for full details: http://www.ctlabs.co.uk/tests/index.html.
Send plasma for thiopental assay in a purple EDTA tube.
The sample must be received in BSUH biochemistry before 14:00h to be sent to Cardiff the same day. Cardiff will process the sample the following morning.
Send the sample to BSUH biochemistry as soon as possible after it is taken where it will be frozen ready for sending.
If serial levels are required it is helpful if the samples can be batched and sent together if possible.

If there is a need for an urgent out of hours or weekend sample Cardiff may be able to help; details are on their website.

Appendix 1

High Dose Thiopental Infusion Patient Suitability Proforma

Name ……

DoB ……

Hospital No ……

Before starting a high dose thiopental infusion please ensure you are familiar with the full guidelines. Complete this form to indicate that all measures to control ICP are in place or have been considered.

		Variance
Has the patient had a CT scan to rule out a surgically treatable lesion?	Yes ☐ No ☐	
Has surgical evacuation of blood/non-viable tissue or decompressive craniectomy been considered if appropriate?	Yes ☐ No ☐ N/A ☐	
Is the patient being nursed 30 degrees head up with optimal head and neck positioning to avoid venous constriction?	Yes ☐ No ☐	
Is patient ventilated with optimal sedation, analgesia and neuromuscular blockade if indicated?	Yes ☐ No ☐	
Is PaO_2 > 13kPa and PCO_2 4.5 – 5kPa	Yes ☐ No ☐	
Is the MAP at a level to achieve CPP>60-70mmHg with volume loading?	Yes ☐ No ☐	
Is Haematocrit 30-35%?	Yes ☐ No ☐	
Has inotropic therapy been initiated if volume loading has not achieved target CPP?	Yes ☐ No ☐	
Has inotropic therapy been increased, within the prescribed limits, to achieve a CPP >60-70mmHg?	Yes ☐ No ☐	
Is the patient's core temperature 36 - 37°C?	Yes ☐ No ☐	
Is the blood glucose between 4.5 – 10mmol/L?	Yes ☐ No ☐	
Has Mannitol +/- hypertonic saline been considered (check plasma osmolality)?	Yes ☐ No ☐	
Has an EVD been considered for CSF drainage?	Yes ☐ No ☐	
If LiCOX in place is the -brain temperature < 37°C & -brain O_2 20 – 40 mmHg	Yes ☐ No ☐ N/A ☐	
Having reviewed the above has the Consultant Neurosurgeon in consultation with the Consultant Intensivist made the decision to start high dose Thiopental?	**Yes ☐ No ☐**	Name of Consultant Neurosurgeon Name of Consultant Intensivist

Completed by:			
Name:	Signature:	Date	Time

Did patient respond to bolus doses of thiopental? Yes ☐ No ☐

Date and time thiopental **started**		Date and time thiopental **stopped**	

Comments

Appendix 2

Administration of High Dose IV Thiopental in Patients with Severe Traumatic Brain Injury with Refractory Raised Intracranial Pressure

Prior to thiopental administration adequately hydrate the patient as hypovolaemia can precipitate severe hypotension.
Patients must have EEG or BIS and continuous cardiac monitoring during administration.
Administer via central venous access device as the preparation has a high pH.[4]
Compatible infusions (assuming they meet close to the vascular access device) [unlicensed]: Cisatracurium, dextrose 5%, dextrose 4%/sodium chloride 0.18%, fentanyl, furosemide, glyceryl trinitrate, heparin sodium, insulin soluble, milrinone, morphine, potassium chloride, propofol and remifentanil. [9]
Incompatible with all other infusions.

Loading dose
Reconstitute 500mg with 20mls water for injection to give a 25mg/mL solution.
Give 250mg in 10mL IV over 5 minutes. Repeat every 15 minutes up to a maximum of 5g (20 boluses) until a reduction in ICP is observed.[10] If the maximum dose has no effect on ICP, do not commence IV infusion.
If a reduction in ICP is seen **along with a reduction in blood pressure** this may indicate impaired autoregulation rather than a response to treatment. Discuss with the Consultant.
If a true reduction in ICP is seen, commence IV infusion.
Hypotension must be avoided. In the event of hypotension consider vasopressors.

IV Infusion [unlicensed]
Reconstitute 3 x 500mg vials with 60mL of water for injection to give a 25mg/mL solution.
Initial Infusion rate 4mg/kg/hour; titrated up to 8mg/kg/hour maximum. [10]
If MAP < 80mmHg stop infusion until MAP≥80mmHg using volume resuscitation or vasopressors.
Supplement low serum potassium cautiously only if ECG changes indicate it

Dose Titration
Titrate infusion rate to achieve an ICP< 25mmHg **and** extensive burst suppression on EEG or a BIS value of 10-20 and a SR of 60-80%. A small amount of electrical activity is desirable to avoid overdosage.
Start at 4mg/kg/hour. Increase if needed to 6mg/kg/hour after 30 minutes.
Increase if needed to maximum dose 8mg/kg/hour after another 30minutes.

Example calculation
To administer 4mg/kg/hour to a 70kg patient using a solution of 1500mg in 60mL (25mg/mL):
Thiopental Infusion rate (mL/hour) = $\frac{4 \text{ mg/kg/hour} \times 70 \text{ kg}}{25 \text{ mg/mL}}$ = **11.2mL/hour**

Using a 1500mg in 60mL (25mg/mL) thiopental solution this table specifies the infusion rate (mL/hr):

Dose →	**4mg/kg/hour**	**6mg/kg/hour**	**8mg/kg/hour**
Patient weight (actual) ↓	Infusion rate		
40kg	6.4mL/hour	9.6mL/hour	12.8mL/hour
60kg	9.6mL/hour	14.4mL/hour	19.2mL/hour
80kg	12.8mL/hour	19.2mL/hour	25.6mL/hour
100kg	16mL/hour	24mL/hour	32mL/hour

Establish Lowest Effective Dose
Once extensive burst suppression is achieved reduce the rate of thiopental by 2mL/hour every 30minutes to find to the lowest dose that will cause burst suppression and maintain ICP < 25mmHg.
If there is no electrical activity on the EEG stop thiopental until the smallest amount of electrical activity returns.
Restart infusion at half previous rate; increase by 2mL/hour every 30mins until **almost** all activity is suppressed.
If Thiopental infusion is effective, stop all other sedation once any paralysing agents have worn off.

Discontinuing the Infusion
Rebound hyperkalaemia may occur upon discontinuation. To minimise the risk of this, reduce the infusion rate by 50% every 2 hours until stopped.

References

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