Pentobarbital Treatment Guidelines for Severe Traumatic Brain Injury

Rationale: Pentobarbital and other barbiturates have been shown in human and animal studies to have neuroprotective effects on patients with traumatic brain injury. This effect appears to be related to their hemodynamic actions. Pentobarbital has been demonstrated to reduce cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) and thus, a reduction in intracranial pressure (ICP). This occurs in a dose-dependent fashion. Studies with pentobarbital as a prophylactic therapy have repeatedly shown no improvement in outcome. The latest guidelines from the Brain Trauma Foundation report a low-quality body of evidence to support the use of high-dose barbiturates to control elevated ICP refractory to maximum medical & surgical treatment. A systematic review published in 2012 reported that in the adult population, though barbiturates reduce ICP, there was no significant evidence that its use is associated with a decrease in death or disability. There is a small body of evidence in the pediatric population showing use of high-dose barbiturates helped to control ICP and was associated with improved long-term outcomes. It therefore continues to be used as a potential salvage therapy for patients with refractory intracranial hypertension. It is essential to ensure that families understand that this treatment is a salvage therapy for injuries associated with very high morbidity and mortality.

Prerequisites for Pentobarbital Initiation:

1. Meets criteria for refractory intracranial hypertension (RICH) after severe Traumatic Brain Injury
    a. Head of Bed maximally elevated
    b. Ventilation and pC02 optimized
    c. At maximal hyperosmolar therapy (Na >160, Osm >330)
    d. Sedation to RASS -5:
        i. Propofol use exhausted for management of elevated ICP
        ii. Dosing up to 80 mcg/kg/min for 1 hour
    e. ICP parameters (*without external interventions/stimuli)*:
        i. ICP 21-35 for 4 hours
        ii. ICP 36-40 for 1 hour
        iii. ICP >40 for 5 minutes
2. Repeat head CT shows no surgically treatable lesions
3. Neurosurgery Consultant without further surgical options and/or agrees with medical coma
4. Palliative care consulted and/or re-consulted upon pentobarbital initiation to help initiate or continue ongoing goals of care discussions & develop treatment boundaries related to pentobarbital, including discussion regarding non-responders and transitioning to comfort care.

Goal of Pentobarbital Treatment: ICP controlled <20 for at least 48 hours

Dosing of Pentobarbital:

1. Start pentobarbital load: 10 mg/kg intravenous bolus over 60 minutes followed by 5mg/kg/hr continuous infusion x 3 hours
2. Decrease PB infusion rate to 1mg/kg/hr and discontinue propofol infusion after completion of load
3. Titrate infusion rate (1-5 mg/kg/hr) to maintain burst suppression goal (2-5 bursts/min).
4. Continue burst suppression for at least 72 hours.
5. After 72 hours of treatment, if ICPs have been controlled for at least 48 hours, begin weaning pentobarbital.
    a. Reduce the dose by 50% every 12 hours until the infusion rate falls below 0.5mg/kg/hr, at which point it should be turned off.
    b. If ICPs become uncontrolled as defined by RICH criteria within the first 12 hours of the infusion being turned off, resume infusion rate which previously achieved goal burst suppression for at least another 48-hour period prior to attempting wean again.

Non-Responder to treatment defined as:

Once goal burst suppression is reached, ICPs persistently uncontrolled at:

1. 21-35 for 4 hours
2. 36-40 for 1 hour
3. >40 for 5 minutes

PB-Responder with failure of treatment defined as:

1. Failure of ICPs to return to <20 in 7 days without pentobarbital
2. Failure of ICPs to normalize after multiple failed weaning attempts
3. Brain death/herniation
4. Severe side effects requiring discontinuation of treatment (hypotension, etc.)

Additional Monitoring:

1. Continuous EEG order *Do not delay initiation of pentobarbital load for EEG setup*
2. Continue monitoring & treatment for hyperosmolar therapy
3. Check LFTs prior to initiation of pentobarbital infusion and then every 72 hours during treatment.
4. Send post-infusion pentobarbital level when unsure if neuro exam is due to residual pentobarbital in the body
    a. Collect 72 hours after discontinuation of infusion
    b. Send out lab – results may be significantly delayed

Potential side effects:

1. Hypotension:
    a. Avoid dopamine as it increases $CMRO_2$
2. Feeding intolerance:
    a. Ileus may persist for up to 7 days after discontinuing pentobarbital
    b. Refer to Nutrition Guidelines, consider early TPN

3. Propylene glycol toxicity
    a. Patients with renal dysfunction prior to PB initiation are at a higher risk for developing propylene glycol toxicity.
    b. Manifestations include: acute renal dysfunction, osmolar gap >10, refractory hypotension, unexplained increases in serum osmol, lactic acidosis, arrhythmias

Revision team:

Bradley M. Dennis, MD	Trauma
Mayur B. Patel, MD, MPH	Trauma
Heather Hart, MSN, AGACNP	Trauma
Jennifer Beavers, PharmD, BCPS	Pharmacy
Lauren Schmidt, PharmD	Pharmacy
Leanne Atkinson, PharmD	Pharmacy
Melissa Smith, MSN, RN	Trauma Performance Improvement

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