PENTOBARBITAL (NEMBUTAL) Protocol

Indications: Uncontrolled elevation of ICP
Seizure activity uncontrolled by other pharmacologic treatments
To decrease cerebral metabolism

Description

Deep anesthesia lowers ICP and decreases the cerebral metabolic usage of oxygen (CMRO2) by altering vascular tone, suppressing metabolism, inhibiting free radical mediated lipid peroxidation, and reducing cerebral blood flow (CBF). This has a beneficial effect on ICP and global cerebral perfusion. Pentobarbital titrated to a burst/suppression pattern on the EEG is used in patients with severe brain injury when intracranial hypertension is refractory to maximal medical and surgical intracranial pressure (ICP) lowering therapy.

However, studies with pentobarbital as a prophylactic therapy have repeatedly shown no improvement in outcome, and 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 Therefore it is essential to ensure that families understand that this treatment is a salvage therapy for injuries associated with very high morbidity and mortality

Note: Refractory intracranial hypertension (RICH) can be defined as intracranial pressure >20 mmHg (*Wakemed >20-22*) for >30 minutes despite head elevation, straightening of the neck, analgesia, sedation, CSF drainage, mannitol and/or hypertonic saline administration.

Key words: Pentobarbital, Refractory Intracranial Hypertension (RICH), Intracranial Pressure (ICP)

Prerequisites

1. Meets criteria for refractory intracranial hypertension **(RICH)** after severe Traumatic Brain Injury (TBI), intracerebral hemorrhage, and or Status Epilepticus
2. Maximized TBI management and provider review of optimal treatment in place.
    a. Head of Bed maximally elevated
    b. Ventilation and pC02 optimized
    c. At maximal hyperosmolar therapy (serum Na >160, serum Osmolality >320)
    d. Sedation and Analgesia maximized (RASS -5, CPOT 0)
        i. Propofol use exhausted for management of elevated ICP
        ii. Dosing up to 80 mcg/kg/min for 1 hour
        iii. ie: Fentanyl dosing at least 150 mcg/hr.
    e. ICP parameters (without external interventions/stimuli):
        i. ICP 21-35 for 4 hours or
        ii. ICP 36-40 for 1 hour or
        iii. ICP >40 for 10 minutes
3. Repeat head CT shows no surgically treatable lesions.
4. Palliative care consult considered by treatment team to discuss ongoing goals of care upon initiation of pentobarbital.

Initiating pentobarbital

1. Verify order-assure the patient has the following supportive equipment:
    a. Mechanical ventilator and pulse oximeter/End tidal CO2 monitor.
    b. Continuous cardiac monitor
    c. Arterial catheter for invasive BP monitoring; consider Flo-Trac.
    d. Central line required
    e. Continuous bedside EEG monitor-
        i. If possible, prior to bolus administration, obtain a 2-minute baseline EEG strip prior to initiation.
        ii. Call Neurodiagnostic (05161) for EEG. (After hours use Rapid Connect for "Neurodiagnostic Tech on Call")
        iii. **Do not delay initiation of pentobarbital loading dose for EEG set up.**
    f. ICP monitor if applicable.

2. Assess the patient's clinical status. Prior to initiating burst/suppression:
    a. Assure ventilatory status is secured by mechanical ventilation. Maintain SpO2 ≥ 95%.
    b. Assure patient is normovolemic.
    c. CPP 60-70 mm Hg is recommended if ICP monitoring in place.

Usual Dosing:

1. Pentobarbital load: refer to **"Pentobarbital Infusion Orders"** order set
    a. Sedatives (including Propofol, Versed, etc.) should be discontinued after completion of loading dose and ICP goals or burst/suppression goals are met.
    b. Recommended: analgesics should be discontinued after loading dose is completed and ICP or burst/suppression goals are met.
    c. Paralytics: should be discontinued after completion of loading dose, no titration needed.
    d. Recommended: Sedatives, analgesics, and/or paralytics should not be restarted while pentobarbital is still infusing.
2. Compatibilities: Do not mix with other drugs.
3. Usual infusion/titration rate (1-4 mg/kg/hr) to maintain burst/suppression goal (TBI-2-3 other <7 bursts/min). ***See order set.***
    a. If EEG activity is suppressed for >2 minutes, and ICP is NOT controlled (ICP range ≤ 22), notify provider, goal is to titrate infusion to burst/suppression not ICP.
    b. If EEG activity does not return, do not titrate lower than starting dose (1mg/kg/hr) without provider notification. (This can be discussed in daily multidisciplinary rounds). *Refer to "Non-Responders" for guidance.*
4. Goals of treatment
    a. Continue burst/suppression for at least 72 hours.
    b. Pentobarbital Treatment: ICP controlled ≤ 22 for at least 48 hours
    c. After 72 hours of treatment, and ICPs controlled for at least 48 hours, begin weaning off pentobarbital per provider order, may discontinue without wean if ordered per providers discretion.
    d. If ICPs become uncontrolled as defined by RICH criteria within the first 12 hours of the infusion being turned off, notify provider for possible restart of infusion.
5. If drip being restarted:
    a. Restart rate at previous dose where appropriate burst/suppression was achieved.
    b. Continue for at least another 48-hour period prior to attempting wean again.

Non-Responders Defined as:

1. "Non-Responder" to treatment defined as: Goal burst/suppression is reached but ICPs persistently uncontrolled at:
    a. 25-35 for 4 hours or
    b. 36-40 for 1 hour or
    c. >40 for 15 minutes
    d. If patient is a non-responder, notify provider and consider discontinuing pentobarbital.
2. Failure of treatment defined as:
    a. Failure of ICPs to normalize after multiple failed weaning attempts.
    b. Brain death/herniation.
    c. Severe side effects requiring discontinuation of treatment (unmanageable hypotension, liver failure, etc.).

Monitoring/Nursing Care

1. Neuro
    a. Pupils may become constricted and fixed. Notify provider for unilateral or bilateral dilation. Blink reflex and cough reflex will be diminished or absent.
    b. Assess pupils q-2h. note: Pupillometer readings will be inconsistent with use of Lacrilube
    c. Lacrilube both eyes, q4 hours. Cover with damp gauze or tape if necessary.
    d. Monitor ICP if present.
    e. Monitor EEG for burst/suppression. Goal is (TBI 2-3 other <7) bursts/min.
2. Respiratory
    a. Due to diminished cough reflex, patient is at great risk for pulmonary sequelae.
    b. Monitor ventilator settings, SpO2, PaO2, and PaCO2/ETCO2.
    c. Chest PT every 2hr. if not contraindicated
    d. **Turn patient at least every 1-2 hours**, and as needed.
    e. Suction patients as indicated.
3. Hemodynamics
    a. Monitor MAP (65-70 mm Hg or SBP > 100 recommended)
    b. CPP (60-70 mm Hg recommended)
    c. Consider FloTrac monitoring.
    d. Norepinephrine recommended
    e. Monitor serum electrolytes q 6 hours or as needed per provider order. Serum NA and or Serum Osmo may be needed more often.
4. Other systems
    a. NG/OG to low intermittent suction.
    b. Maintain normothermia 36 – 37.5°C. (96.8-99.5°F); recommend continuous temperature monitoring.
    c. DVT prophylaxis (SCD's and/or pharmacological).
    d. Skin assessment and care prn and document on flow sheet.

Nursing Documentation:

a. Document baseline EEG activity if possible
b. Document EEG q 30 min
c. Document Vital signs, ICP, CPP, and neuro assessments at least q1hr

Nursing Considerations:

a. Prior to loading dose of pentobarbital, ensure order to discontinue all sedation, analgesia, and paralytic infusions.
b. If ICP or seizure activity controlled without goal burst/suppression, there is no need to increase drip. ***Note: Some patients never reach EEG suppression.***
c. If EEG activity is suppressed for >2 minutes and ICP is NOT controlled (ICP range ≤20-22), notify physician, goal is to titrate infusion to burst/suppression not ICP.
c. See Pentobarbital Coma related policies Nursing Systemwide-Critical Care EEG Monitoring v.2 (navexone.com) for other care recommendations.

Additional Monitoring Considerations:

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. After pentobarbital is discontinued, send post-infusion pentobarbital level when unsure if neuro exam is due to residual pentobarbital in the body.
    a. Send out lab – results may be significantly delayed.
        i. Pentobarbital levels > 10mcg/ml have been associated with toxicity.
        ii. Therapeutic levels for Intracranial pressure therapy can be as high as 30-40 mcg/ml
    b. **Clinical Brain death** criteria can't be assessed until level < 10 mcg/ml.

    Note: However, a nuclear brain flow study can be used to make the determination of brain death as it remains definitive in the setting of pentobarbital use.

Potential Side Effects

1. Hypotension:
    a. Avoid dopamine as it increases cerebral metabolic rate ($CMRO_2$)
2. Feeding intolerance:
    a. Ileus risk may persist for up to 7 days after discontinuing pentobarbital.
    b. Consider early TPN.
3. Propylene glycol toxicity
    a. Patients with renal dysfunction prior to pentobarbital 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.
4. Pentobarbital induced hypokalemia
    a. Monitor potassium levels frequently, during and after infusion
    b. Levels as low as 3.0mmol/l in the absence of cardiac arrhythmias may be appropriate.
    c. Monitor for rebound hyperkalemia when d/c infusion and or aggressive replacements.
5. Multi-system organ failure
6. Other
    a. Laryngospasm
    b. Bronchospasm
    c. Pulmonary edema

APPENDIX A: Initial Pentobarbital (Nembutal) Infusion Algorithm

References

Awad, M., Bonitz, J., & Pratt, A. (2020). Pentobarbital Induced Hypokalemia: A Worrying Sequela. *International Journal of Surgery Case Reports, 71,* 323-326. 10.1016/j.ijscr.2020.05.032

Battaglini, D., Anania, P., Rocco, P. R. M., Brunetti, I., Prior, A., Zona, G., Pelosi, P., & Fiaschi, P. (2020). Escalate and De-Escalate Therapies for Intracranial Pressure Control in Traumatic Brain Injury. *Frontiers in Neurology, 11,* 564751. 10.3389/fneur.2020.564751

Carney, N., Totten, A. M., O'Reilly, C., Ullman, J. S., Hawryluk, G. W. J., Bell, M. J., Bratton, S. L., Chesnut, R., Harris, O. A., Kissoon, N., Rubiano, A. M., Shutter, L., Tasker, R. C., Vavilala, M. S., Wilberger, J., Wright, D. W., & Ghajar, J. (2016). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery, 80*(1), 6-15. 10.1227/NEU.0000000000001432

Dennis, B., Patel, M., Hart, H., Beavers, J., Schmidt, L., Atkinson, L., & Smith Melissa. (2018). *Pentobarbital Treatment Guidelines for Severe Traumatic Brian Injury*. Vanderbilt Medical Center.

Donnelly, J., Czosnyka, M., Adams, H., Robba, C., Steiner, L. A., Cardim, D., Cabella, B., Liu, X., Ercole, A., Hutchinson, P. J., Menon, D. K., Aries, M. J. H., & Smielewski, P. (2017). Individualizing thresholds of cerebral perfusion pressure using estimated limits of autoregulation. Critical Care Medicine, 45(9), 1464-1471. https://doi.org/10.1097/CCM.0000000000002575

EISENBERG, H. M., FRANKOWSKI, R. F., CONTANT, C. F., MARSHALL, L. F., & WALKER, M. D. (1988). High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *Journal of Neurosurgery, 69*(1), 15-23. 10.3171/jns.1988.69.1.0015

Frohlich, J., Johnson, M. A., McArthur, D. L., Lutkenhoff, E. S., Dell'Italia, J., Real, C., Shrestha, V., Spivak, N. M., Ruiz Tejeda, J. E., Vespa, P. M., & Monti, M. M. (2021). Sedation-Induced Burst Suppression Predicts Positive Outcome Following Traumatic Brain Injury. *Frontiers in Neurology, 12*, 750667. 10.3389/fneur.2021.750667

Hickey, J. V., & Strayer, A. (2019). *The clinical practice of neurological and neurosurgical nursing* (Eighth ed.). Wolters Kluwer.

Jahns, F., Miroz, J. P., Messerer, M., Daniel, R. T., Taccone, F. S., Eckert, P., & Oddo, M. (2019). Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. Critical Care (London, England), 23(1), 155-155. https://doi.org/10.1186/s13054-019-2436-3

PENTobarbital. *Lexi-Drugs*. Lexicomp Online [database online]. Hudson, OH: Wolters Kluwer Clinical Drug Information Inc; 2018.

Marshall, G. T., James, R. F., Landman, M. P., O'Neill, P. J., Cotton, B. A., Hansen, E. N., Morris, J. A., & May, A. K. (2010b). Pentobarbital Coma for Refractory Intra-Cranial Hypertension After Severe Traumatic Brain Injury: Mortality Predictions and One-Year Outcomes in 55 Patients. *The Journal of Trauma, 69*(2), 275-283. 10.1097/TA.0b013e3181de74c7

Roberts, I., & Sydenham, E. (2012). Barbiturates for acute traumatic brain injury. *Cochrane Database of Systematic Reviews, 12*(12), CD000033. 10.1002/14651858.CD000033.pub2

Ryan, D. (2019). *Handbook of neuroscience nursing: care of the adult neurosurgical patient*.

Smedley, L. W., Rios, D., Barthol, C. A., & Garvin, R. E. (2019). Iatrogenic Propylene Glycol Intoxication Due to High-Dose Pentobarbital for Refractory Intracranial Hypertension: A Case Report. *Journal of Pharmacy Practice, 33*(6), 895-898. 10.1177/0897190019854575

Svedung Wettervik, T., Howells, T., Lewén, A., & Enblad, P. (2020;2019;). Blood pressure variability and optimal cerebral perfusion Pressure—New therapeutic targets in traumatic brain injury. Neurosurgery, 86(3), E300-E309. https://doi.org/10.1093/neuros/nyz515

Theodore, D., & Mahanes, D. (2019). Barbiturate-induced dyskalaemia in patients with traumatic brain injury patient. *BMJ Case Reports, 12*(4), e228119. 10.1136/bcr-2018-228119

Vella, M. A., Crandall, M. L., & Patel, M. B. (2017). Acute Management of Traumatic Brain Injury. *The Surgical Clinics of North America, 97*(5), 1015-1030. 10.1016/j.suc.2017.06.003

APPENDIX A: Initial Pentobarbital (Nembutal) Infusion Algorithm