**Increased Intracranial Pressure  Introduction**

Increased intracranial pressure (ICP) is a potentially life-threatening condition that requires prompt recognition and treatment. It occurs when the volume of the brain parenchyma, blood, or cerebrospinal fluid rises, resulting in elevated pressure within the skull. The normal ICP range is 5-15 mmHg in adults and 3-7 mmHg in children. An ICP above 20-25 mmHg for over 5 minutes is considered elevated and interventions should be implemented to prevent herniation and irreversible neurological damage. Increased ICP is commonly seen in traumatic brain injury, strokes, tumors, infections, and hemorrhages.

As clinical pharmacists, it is essential to have a comprehensive understanding of this disease state as it plays a crucial role in the management of patients. Increased intracerebral pressure occurs when there is an abnormal increase in pressure within the skull, leading to potentially severe consequences. This chapter will delve into the clinical presentation, pathophysiology, diagnostic approach, and management strategies for increased intracerebral pressure. By familiarizing ourselves with these key aspects, we can contribute to optimizing patient outcomes and ensuring the safe and effective use of pharmacotherapy.

**Clinical Presentation**

The clinical presentation of increased intracranial pressure can vary significantly depending on the underlying etiology, rate of progression, and severity. However, there are some common signs and symptoms that may indicate elevated ICP and prompt urgent evaluation and treatment.

* Headache - Often described as throbbing or diffuse, worsens with exertion or Valsalva. May be accompanied by nausea/vomiting. Can be the only symptom of chronically elevated ICP.
* Altered mental status - Manifests as confusion, drowsiness, or loss of consciousness. May fluctuate or progress rapidly. Concerning for cerebral herniation if associated with lateralizing neurologic deficits.
* Vision changes - Diplopia from cranial nerve palsies, blurry vision from papilledema. Patients may describe curtains/halos in their visual fields.
* Ataxia, dizziness - Results from compression of cerebellum or brainstem. Worrisome for impending herniation.
* Nausea/vomiting - Can be an early symptom, related to stimulation of the vomiting center in the medulla by pressure.
* Seizures - More common with rapidly increasing ICP.
* Focal neurological deficits - Weakness, sensory changes depending on localized effects of mass lesions or herniation syndromes.
* Cushing's triad - Bradycardia, hypertension, irregular respiration is a late finding indicating impeded cerebral perfusion.

Risk Factors:

* Traumatic brain injury - Contusions, bleeds, or cerebral edema can manifest rapidly after injury
* ICH, SAH, AVM - Hemorrhagic strokes increase volume acutely
* Brain tumors - Mass effect or obstruction of CSF flow causes increased ICP
* CNS infections - Inflammation and edema related to meningitis/encephalitis
* Acute hydrocephalus - Intraventricular hemorrhage or meningitis prevents CSF absorption
* Hypertensive encephalopathy - Cerebral edema from failed autoregulation of blood flow
* Fulminant hepatic failure - Cytotoxic edema from accumulating ammonia and glutamine
* High altitude sickness - Hypoxemia leads to cerebral vasodilation and increased blood volume

Patients with acute neurological injuries or disorders affecting the brain are at highest risk. Increased ICP can occur at any age but is more common in adults. The clinical progression can vary from insidious headache to rapid neurological decline depending on the underlying process. Early recognition of signs and symptoms in at-risk patients is key to prevent further brain injury.

**Pathophysiology**

The pathophysiology of increased ICP depends on the underlying cause but ultimately involves an increase in one or more of the intracranial components (brain parenchyma, blood, or cerebrospinal fluid).

* Cytotoxic edema: Cellular dysfunction leads to intracellular fluid accumulation and swelling of brain cells. Seen in ischemia, trauma, and metabolic disorders.
* Vasogenic edema: Disruption of the blood-brain barrier allows extracellular fluid accumulation. Seen with tumors, abscesses, hemorrhage, and inflammation.
* Hydrocephalus: Decreased CSF reabsorption leads to ventricular enlargement and increased CSF volume. Seen with hemorrhage, meningitis, or obstructing mass lesions.
* Increased cerebral blood flow: Vascular engorgement increases cerebral blood volume. Seen with impaired autoregulation.
* Space-occupying lesions: Mass effect physically compresses brain tissue and displaces CSF/blood. Seen with hemorrhages, tumors, etc.

As the cranial vault has a fixed volume, the increased volume of one of the intracranial components leads to elevated ICP. The Monroe-Kellie doctrine states that the sum of volumes must remain constant.

If the compensatory mechanisms (displacement of CSF/blood) are overwhelmed, brain tissue herniates through rigid dural partitions and compresses vital centers in the brainstem. This is life-threatening.

**Diagnostic Approach**

The diagnostic approach for patients presenting with increased intracerebral pressure involves a combination of clinical evaluation, imaging studies, and monitoring techniques. The primary goal is to assess the severity of intracranial pressure (ICP) and identify the underlying cause. The diagnostic process may vary depending on the subtype of increased intracerebral pressure, and the specific tests and criteria used may differ accordingly. Here is an overview of the diagnostic approach:

**Clinical Evaluation:**

* Detailed history taking to understand the patient's symptoms, medical history, and potential risk factors.
* Physical examination to assess neurological status, including mental status, cranial nerve function, motor strength, reflexes, and sensory perception.
* Evaluation of vital signs, such as blood pressure, heart rate, and respiratory rate, which may provide clues about the severity of intracranial hypertension.

**Imaging Studies:**

* Computed Tomography (CT) scan: This is usually the initial imaging modality used to evaluate the brain for structural abnormalities, such as hemorrhage, tumors, or edema.
* Magnetic Resonance Imaging (MRI): In some cases, an MRI may be performed to obtain more detailed information about brain pathology, especially in non-emergent situations.
* Cerebral Angiography: If vascular abnormalities or suspected vasospasm are present, cerebral angiography may be performed to visualize the blood vessels and assess blood flow.

**Monitoring Techniques:**

* Intracranial Pressure (ICP) Monitoring: Invasive ICP monitoring may be utilized in critically ill patients to continuously measure and manage ICP. This involves placing a catheter or probe into the brain parenchyma or ventricles to directly measure pressure.
* Transcranial Doppler (TCD): TCD ultrasound can be used to assess cerebral blood flow velocities, providing information about cerebral perfusion and potential vasospasm.

It is important to note that the diagnostic approach may differ for specific subtypes of increased intracerebral pressure, such as traumatic brain injury, intracerebral hemorrhage, or hydrocephalus. For example, additional tests like laboratory studies (e.g., coagulation profile, blood gas analysis) or lumbar puncture may be necessary in certain scenarios to rule out specific underlying causes or complications.

**Management – Overview**

The management of increased intracerebral pressure involves a multifaceted approach, including non-pharmacologic and pharmacologic interventions. The primary goals of treatment are to reduce intracranial pressure, maintain cerebral perfusion pressure, and prevent secondary brain injury. Non-pharmacologic measures include surgical decompression, hyperventilation, prophylactic hypothermia, and nutrition optimization. Pharmacotherapy plays a crucial role, with osmotic agents such as mannitol and hypertonic saline being commonly used. Additionally, anesthetics, analgesics, sedatives, and steroids may be employed to control pain, agitation, and inflammation. The choice of management strategies depends on the underlying cause, severity of symptoms, and individual patient characteristics. Close monitoring and adjustments are necessary to ensure optimal patient outcomes.

**Pharmacotherapy**

In the management of increased intracerebral pressure, pharmacotherapy plays a crucial role in reducing brain edema and stabilizing intracranial pressure (ICP). Here is a comprehensive overview of pharmacological interventions, including first-line and alternative therapies, their mechanisms of action, dosing considerations, side effects, contraindications, monitoring parameters, and clinical pearls. This information will be valuable for clinical pharmacists preparing for board certification exams.

1. First-Line Therapies:

a. Osmotic Agents:

* Mannitol:
  + Mechanism of Action: Mannitol is an osmotic diuretic that creates an osmotic gradient, drawing water from brain tissue into the bloodstream, thereby reducing brain edema and ICP.
  + Dosing and Administration:
    - Initial dose: 0.25 to 1 gram per kilogram of body weight as an intravenous bolus over 5-10 minutes.
    - Maintenance dose: May repeat the bolus dose or administer as an infusion at 0.25 to 0.5 grams per kilogram of body weight every 4-6 hours.
  + Side Effects:
    - Osmotic diuresis leading to volume depletion and potentially hypotension, electrolyte imbalances (e.g., hypernatremia, hypokalemia), and potential exacerbation of heart failure.
  + Contraindications:
    - Renal dysfunction, pre-existing volume overload, active intracranial bleeding.
  + Monitoring Parameters:
    - Urine output, serum osmolality, electrolytes (especially sodium and potassium), renal function, and hemodynamic status.

b. Hypertonic Saline (HTS):

* Mechanism of Action: Hypertonic saline increases serum osmolality, drawing water out of brain tissue and reducing brain edema and ICP.
* Dosing and Administration:
  + Concentrations: 3% or 23.4% hypertonic saline solutions.
  + Initial dose: 2 to 5 mL/kg of 3% or 23.4% 30-45 ml solution as an intravenous bolus over 5-10 minutes.
  + Side Effects:
    - Hypernatremia, hypervolemia, electrolyte imbalances, and potential exacerbation of heart failure.
  + Contraindications:
    - Pre-existing hypernatremia, severe congestive heart failure, or renal impairment.
  + Monitoring Parameters:
    - Serum sodium levels, volume status, renal function, and hemodynamic parameters.
  + Administration
    - 3% has been consistently shown to be safely administered though a large bore peripheral IV
    - Emergening data is available with 23% NaCl being administered through a peripheral line but more data is needed for routine adoption into guidelines

2. Alternative Therapies:

a. Barbiturates:

* Thiopental or Pentobarbital:
  + Mechanism of Action: Barbiturates act as central nervous system depressants, reducing cerebral metabolic rate, neuronal activity, cerebral blood flow (CBF), and ICP.
  + Dosing and Administration:
    - Thiopental: Initiate at 3-5 mg/kg followed by an infusion of 1-5 mg/kg/hour.
    - Pentobarbital: Initiate at 5-10 mg/kg followed by an infusion of 1-10 mg/kg/hour.
  + Side Effects:
    - Hypotension, cardiac depression, respiratory depression, immunosuppression, metabolic derangements, prolonged sedation, and delayed awakening after discontinuation.
  + Contraindications:
    - Hypersensitivity to barbiturates, pregnancy, severe hepatic dysfunction, and respiratory insufficiency.

3. Additional Considerations:

a. Non-Pharmacologic Therapies:

* Hyperventilation: Reduces ICP by causing vasoconstriction and decreasing cerebral blood volume. Used as a temporizing measure.
* Prophylactic hypothermia: Cooling to 32-34°C may help reduce ICP and cerebral metabolism.
* Therapeutic normothermia: Maintaining normothermia helps avoid exacerbations of ICP from fever.
* Nutrition optimization: Meeting caloric needs helps prevent protein breakdown and catabolism.
* Surgical decompression: Craniectomy or hematoma evacuation removes mass effect or provides space for swelling.

b. Clinical Pearls:

* Continuous monitoring of ICP, cerebral perfusion pressure (CPP), and hemodynamic parameters is essential for titrating pharmacotherapy and assessing treatment response.
* Individualize dosing based on patient characteristics, underlying pathology, and response to therapy.
* Regular assessment of electrolyte levels, renal function, and fluid balance is crucial to maintain optimal patient status.
* Collaborate with the healthcare team to ensure appropriate patient selection, monitoring, and management of potential adverse effects.

c. Differences in Treatment Approaches for Subtypes:

* Traumatic Brain Injury (TBI): Prompt initiation of osmotic agents, such as mannitol or hypertonic saline, in the emergency setting is crucial to reduce brain edema and ICP.
* Intracerebral Hemorrhage: Careful consideration of blood pressure management and avoidance of aggressive blood pressure control to maintain cerebral perfusion.
* Hydrocephalus: Management may involve surgical interventions, such as ventriculostomy or shunt placement, in addition to pharmacotherapy for controlling ICP.

**Key Guidelines and Evidence**

Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients

The main pharmacologic interventions recommended include:

* Use symptom-based bolus dosing of hypertonic sodium solutions rather than sodium target-based dosing for managing elevated ICP or cerebral edema in patients with subarachnoid hemorrhage.
* Use hypertonic sodium solutions over mannitol for initial management of elevated ICP or cerebral edema in patients with traumatic brain injury.
* Use either hypertonic sodium solutions or mannitol for initial management of elevated ICP or cerebral edema in patients with acute ischemic stroke.
* Use hypertonic sodium solutions over mannitol for managing elevated ICP or cerebral edema in patients with intracerebral hemorrhage.
* Avoid corticosteroids in patients with intracerebral hemorrhage given increased risk of mortality and infections.
* Monitor osmolar gap over serum osmolarity thresholds during treatment with mannitol to assess risk of acute kidney injury.

Evidence

Here is a summary of the key studies comparing hypertonic saline (HTS) and mannitol for reducing intracranial pressure (ICP) in traumatic brain injury (TBI) patients:

Study Design & Size:

* Kerwin et al. 2009 - Retrospective analysis, n=22 patients
* Burgess et al. 2016 - Meta-analysis, 7 trials, n=191 patients

Intervention and Outcomes:

* Kerwin et al. - HTS vs mannitol for mean ICP reduction in TBI patients
  + HTS more effective at reducing ICP than mannitol
* Burgess et al. - HTS vs mannitol for mean ICP reduction, ICP treatment failure, mortality, neurological outcomes
  + No difference in ICP reduction, mortality, or neurological outcomes
  + Decreased risk of ICP treatment failure with HTS vs mannitol

Key Takeaways:

* Evidence suggests HTS is at least as effective, if not more effective, than mannitol for reducing ICP in TBI patients
* HTS may lead to lower risk of ICP treatment failure compared to mannitol
* No clear differences demonstrated in mortality or neurological outcomes
* Overall, HTS appears to be a suitable alternative, if not preferred agent, over mannitol for ICP reduction in TBI

**Clinical Scenarios**

Scenario 1

A 42-year-old male is brought to the emergency department following a motor vehicle accident. His Glasgow Coma Scale is 9 and he has right-sided hemiparesis. A CT scan reveals a large left frontal hematoma with midline shift. Neurosurgery plans to take him urgently to the OR for hematoma evacuation. His blood pressure is 142/88 mm Hg, heart rate 92 bpm, respiratory rate 14, and oxygen saturation 97% on room air. The team asks if they should administer mannitol prior to surgery to reduce ICP.

In this case, mannitol administration would provide little benefit and poses unnecessary risks given he will soon undergo definitive surgical management of the hematoma and elevated ICP. Pre-operative mannitol may deplete his intravascular volume and cause electrolyte disturbances, which could be detrimental prior to surgery. Close neurological monitoring is warranted to ensure he does not show signs of herniation.

Scenario 2

A 32-year-old female with a brain tumor is admitted to the ICU with a GCS of 8. She has an external ventricular drain (EVD) set at 20 mmHg. Opening pressure on admssion was 35 mmHg. Her neuro exam shows pupils equal and reactive. Labs are unremarkable. She receives a dose of mannitol and her ICPtrends down to 10-15 mmHg. Two hours later, the ICU nurse notes bradycardia to 40 bpm and hypertension of 168/102 mmHg.

This patient shows signs of Cushing's triad indicating impeded cerebral perfusion from increased ICP. Despite recent mannitol, it appears the ICP is rising again. The EVD should be checked for patency. Additional CSF drainage and another dose of mannitol should be given. Hyperventilation can serve as a temporizing measure as well. Her neuro exam and vitals should be monitored closely.

Scenario 3

A 67-year-old male with a large ischemic stroke is receiving scheduled mannitol doses. His serum sodium is 154 mEq/L and measured serum osmolality is 320 mOsm/kg. Urine output has declined over the past few hours. How should this patient be managed?

The patient's electrolytes and renal function should be closely monitored when receiving mannitol. An osmolality gap greater than 20 mOsm/kg H2O suggests mannitol accumulation which can cause renal injury. In addition, the high serum sodium puts him at risk for osmotic demyelination syndrome if fluids are replaced too rapidly. Mannitol should be held and serum electrolytes rechecked. Fluids with low sodium content should be used to avoid overly rapid correction when replacing his urine output. Renal function should be monitored.

**Increased Intracranial Pressure Summary**

Increased intracerebral pressure is a critical condition that requires prompt and effective management. Pharmacotherapy plays a crucial role in reducing brain edema and stabilizing intracranial pressure (ICP). First-line treatments include osmotic agents like mannitol and hypertonic saline, while barbiturates are reserved for refractory cases. Individualized dosing, close monitoring of electrolytes and renal function, and consideration of comorbidities are essential. Guidelines from organizations like the Brain Trauma Foundation provide evidence-based recommendations. Clinical pharmacists play a vital role in optimizing medication regimens and ensuring patient safety.

**References**

1. Stocchetti N, Maas AIR. Traumatic intracranial hypertension. N Engl J Med. 2014;370(22):2121-2130. doi:10.1056/NEJMra1208708
2. Carney N, Totten AM, O’Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80(1):6-15. doi:10.1227/NEU.0000000000001432
3. Jain KK. Textbook of Hyperbaric Medicine, 6th ed. Cham, Switzerland: Springer; 2017.
4. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69(5):1037-1045. doi:10.1227/NEU.0b013e3182289f81
5. Diringer MN, Bleck TP, Claude Hemphill J 3rd, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211-240. doi:10.1007/s12028-011-9605-9
6. Cottenceau V, Masson F, Mahamid E, et al. Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma. 2011;28(10):2003-2012. doi:10.1089/neu.2011.1885
7. Rozet I, Tontisirin N, Muangman S, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology. 2007;107(5):697-704. doi:10.1097/01.anes.0000287029.84358.5d
8. Ichai C, Armando G, Orban JC, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med. 2009;35(3):471-479. doi:10.1007/s00134-008-1293-9
9. Brain Trauma Foundation. Guidelines for prehospital management of traumatic brain injury. Prehosp Emerg Care. 2008;12 Suppl 1:S1-S52. doi:10.1080/10903120701732052
10. Adelson PD, Wisniewski SR, Beca J, et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. Lancet Neurol. 2013;12(6):546-553. doi:10.1016/S1474-4422(13)70077-2
11. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. Pediatr Crit Care Med. 2012;13 Suppl 1(Suppl 1):S1-S82. doi:10.1097/PCC.0b013e31825fb86c
12. Faiver L, Hensler D, Rush SC, Kashlan O, Williamson CA, Rajajee V. Safety and Efficacy of 23.4% Sodium Chloride Administered via Peripheral Venous Access for the Treatment of Cerebral Herniation and Intracranial Pressure Elevation. Neurocrit Care. 2021 Dec;35(3):845-852. doi: 10.1007/s12028-021-01248-7. Epub 2021 Jun 25. PMID: 34173156.
13. Cook AM, Morgan Jones G, Hawryluk GWJ, Mailloux P, McLaughlin D, Papangelou A, Samuel S, Tokumaru S, Venkatasubramanian C, Zacko C, Zimmermann LL, Hirsch K, Shutter L. Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients. Neurocrit Care. 2020 Jun;32(3):647-666. doi: 10.1007/s12028-020-00959-7. PMID: 32227294; PMCID: PMC7272487.
14. Kerwin AJ, Schinco MA, Tepas JJ 3rd, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma. 2009 Aug;67(2):277-82. doi: 10.1097/TA.0b013e3181acc726. PMID: 19667879.
15. Burgess S, Abu-Laban RB, Slavik RS, Vu EN, Zed PJ. A Systematic Review of Randomized Controlled Trials Comparing Hypertonic Sodium Solutions and Mannitol for Traumatic Brain Injury: Implications for Emergency Department Management. Ann Pharmacother. 2016 Apr;50(4):291-300. doi: 10.1177/1060028016628893. Epub 2016 Jan 29. PMID: 26825644.