Chapter 13
Drugs and the Central Nervous System

Mohd Shahnaz Hasan

Abstract As in all other organ systems, prevention of hypoxia is the aim in the management of central nervous system pathology, to prevent or minimize secondary brain damage and neuronal dysfunction. In the normal brain, auto-regulation, oxygen and carbon dioxide levels are the main determinants of cerebral blood flow. Once the physiological regulatory conditions have been breached, such as in trauma, bleeding or infection, the intracranial pressure rises and caregivers intervene to maintain adequate oxygenation and ventilation, and try to ensure that cerebral blood flow (and thus oxygen delivery) is adequate to meet the metabolic demand of the brain. This is more crucial in the brain than in any other organ in the body because its high metabolic requirements render the brain extremely sensitive to hypoxic conditions. The drugs used are mainly to modulate cerebral metabolism, cerebral perfusion pressure, cerebral blood flow and brain volume (cerebral edema). Adequate knowledge of cerebral physiology and the pharmacological effects of these drugs is vital to provide optimum care in patients with cerebral pathology.

Keywords Intracranial pressure • Cerebral blood flow • Cerebral metabolism • Cerebral perfusion pressure • Brain damage • Neuronal dysfunction

Introduction

Due to the high metabolic demand of the brain (20 % of total body oxygen consumption at rest), it is extremely sensitive to hypoxic conditions. Besides being the center of control of our voluntary functions, it is also the seat of our consciousness, intellect and personality; so any damage to our brain could result in a loss of physical function as well as a loss of 'self'. Thus, safeguarding the integrity of the brain is the prime objective of medical practice.

Brain tissue, cerebrospinal fluid (CSF) and blood are the main components within a rigid skull of fixed volume. Any increase in any of the components, unless accompanied by a corresponding decrease in one or more of the other components,

M.S. Hasan, M.B.B.S., M.Anaes (✉)
Department of Anesthesiology, Faculty of Medicine, University of Malaya,
50603 Kuala Lumpur, Malaysia
e-mail: shahnaz@ummc.edu.my

Y.K. Chan et al. (eds.), *Pharmacological Basis of Acute Care*,
DOI 10.1007/978-3-319-10386-0_13

leads to an increase in intracranial pressure, which eventually leads to a decrease in cerebral blood flow. Pharmacological agents that can influence these three components play a vital role, either directly or indirectly, in ensuring adequate oxygen and glucose supply to the brain and hence the brain integrity. Caregivers managing patients with cerebral pathology in the acute care setting should have adequate knowledge and thorough understanding of cerebral physiology and its alteration by certain drugs.

The main aim in management is to ensure that oxygen supply matches demand. Secondary brain damage resulting from ischemia is then minimized and ultimately neuronal function can be preserved. Pharmacotherapy can be used to decrease the metabolism and oxygen demands of the brain. Drugs can also be used to maintain cerebral blood flow through the control of cerebral perfusion pressure (CPP) and the caliber of cerebral vessels. In situations of brain injury and hypoxia, brain mass increases due to edema, increasing the intracranial pressure (ICP). This can be managed pharmacologically with the use of diuretics. Currently, drugs altering the mechanics of CSF production and absorption are not available for clinical use.

Drugs Modulating Cerebral Metabolism

In health, cerebral blood flow (CBF) is closely coupled to the metabolic activity of the brain. This is expressed as the cerebral metabolic rate for oxygen ($CMRO_2$) and is constant at 3.5 ml/100 g/min. This is to allow sufficient delivery of oxygen and glucose to the brain in order to meet the energy demands of the brain.

In brain injured patients, pharmacological agents that can reduce the $CMRO_2$ are often utilized so that the oxygen/energy needs can still be met in the face of decreased oxygen delivery because of decreased cerebral blood flow (Fig. 13.1).

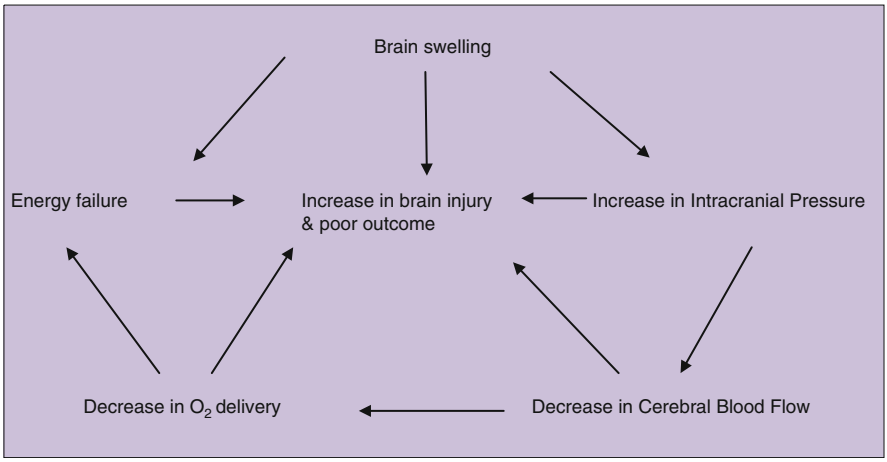

Fig. 13.1 Escalating cycle of brain swelling resulting in energy failure, increase in brain damage and poor outcome following injury to the brain (With permission of Wolters Kluwer Health; Decompressive craniectomy in head injury. Curr Opin Crit Care 2004: 10(2):101–4)

These agents mainly involve anesthetic drugs such as propofol, barbiturates and benzodiazepines. Volatile anesthetics reduce $CMRO_2$ while also exerting a dose-dependent vasodilatory effect on cerebral vessels that increases CBF.

Conversely, seizures and hyperthermia will increase $CMRO_2$ and subsequently CBF and ICP. If not treated appropriately, both conditions are associated with poorer outcome after successful cardiopulmonary resuscitation. Antipyretics such as acetaminophen can be used to manage hyperthermia, as well as physical methods of cooling. Seizures can be controlled with antiepileptics like phenytoin, benzodiazepine and barbiturates.

Propofol

This is a commonly used drug in anesthesia and critical care, mainly as an induction agent and in total intravenous anesthetic technique in neuroanesthesia. It is also used as a sedative agent in critically ill patients especially in neurocritical care unit to provide cerebral protection. Propofol decreases the cerebral metabolic rate for oxygen ($CMRO_2$), which leads to a reduction in CBF and ICP. However, one must be cautious when large doses are being used as it may result in systemic hypotension that will further compromise the CPP. Propofol is known to cause myoclonus but is non-epileptogenic, and is sometimes used to treat refractory status epilepticus.

Thiopental

Thiopental is less commonly used nowadays due to its unfavorable pharmacokinetic profile. It decreases $CMRO_2$ and causes cerebral vasoconstriction which result in reduced CBF, cerebral blood volume (CBV) and ICP. Thiopental can cause significant hypotension, which can impair CPP. It is sometimes used in selected cases with refractory elevated ICP to produce a state of deep coma when other conventional therapies failed to reduce ICP. Induced coma with the use of barbiturates like thiopental is called barbiturate coma.

Benzodiazepines

Agents in this category such as midazolam are widely used as sedative agents in neurocritical care unit. Its effect on cerebral physiology is similar to the above drugs, but to a lesser degree, with a less significant drop in $CMRO_2$, CBF, CBV and ICP.

Drugs Modulating Cerebral Blood Flow

Cerebral blood flow (CBF) is affected mainly by oxygen and carbon dioxide tensions in the blood and by autoregulation. CBF under normal conditions is maintained at a relatively constant rate despite variations in CPP. The mechanism involves alteration in the cerebral vascular resistance by changing the diameter of the cerebral arterioles. This phenomenon is known as autoregulation (Fig. 13.2). CBF is held constant over the CPP range of 50–150 mmHg. At the upper limit, the arterioles are maximally vasoconstricted and any increase in CPP will result in increased CBF. At the lower limit, the arterioles are maximally dilated in an attempt to maintain CBF, below which CBF becomes pressure dependent.

Cerebral perfusion pressure (CPP) depends on the mean arterial pressure (MAP) and the ICP or jugular venous pressure (JVP), whichever is greater, whereby

$$\text{CPP} = \text{MAP} - \text{ICP} \qquad \text{or} \qquad \text{CPP} = \text{MAP} - \text{JVP}$$

Many conditions can affect this autoregulatory process, which includes traumatic brain injury, hemorrhage, infection, tumor and certain pharmacological agents. Cerebral blood flow can be controlled by manipulating the mean arterial pressure and by changing the caliber of the cerebral blood vessels.

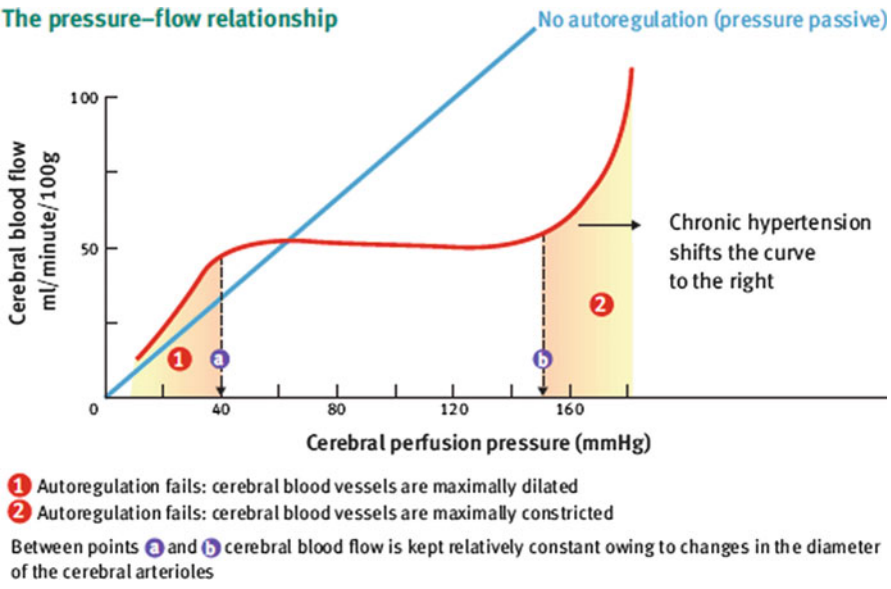

Fig. 13.2 Autoregulation of blood flow in the brain depending on cerebral perfusion pressure (With permission from Surgery (Oxford); Applied physiology of the CNS Surgery 2005; 23 (1):7–12)

Drugs Affecting Mean Arterial Pressure

From the equation above, agents that increase mean arterial pressure will also increase cerebral perfusion pressure, which may help to maintain cerebral blood flow. So, drugs which are used to support the cardiovascular system by increasing the mean arterial pressure (see Chap. 11) are often used to try to improve cerebral blood flow in conditions of raised ICP. In the adult brain, the CPP is normally between 70 and 90 mmHg.

Drugs Affecting Caliber of Cerebral Blood Vessels

Drugs which alter the radius of cerebral blood vessels are not commonly used to improve cerebral blood flow and oxygenation in cases of brain injury. The following drugs are used in the management of brain injury in specific situations.

Nimodipine

Nimodipine, a cerebro-selective calcium channel blocker is administered prophylactically to prevent the development of cerebral vasospasm in patients who present with subarachnoid hemorrhage (SAH) due to ruptured aneurysm. Its use has been associated with improved outcome but mortality remains unchanged. It reduces the influx of calcium through the L-type calcium channels in smooth-muscle cells leading to decreased smooth-muscle contraction resulting in reduced arterial narrowing. In more recent studies, nimodipine has been applied intra-arterially for the treatment of refractory cerebral vasospasm.

Volatile or Inhalational Anesthetics

Volatile anesthetic agents are generally used only in the anesthetic management of brain injury, but will be mentioned here because of their significant effects on the brain. These agents are known to cause a dose-dependent rise in CBF as a result of cerebral vasodilation, which can lead to increase in CBV and ICP. Commonly used anesthetic agents such as isoflurane, sevoflurane and desflurane also cause a reduction in the $CMRO_2$, which leads to an uncoupling of flow and metabolism which is also concentration-dependent. Cerebral vascular reactivity to carbon dioxide and autoregulation are generally preserved but are gradually abolished by increasing concentration of volatile anesthetic agents. Enflurane at high concentrations and in the presence of hypocarbia causes epileptiform activity on electroencephalography, thus is not commonly used in neuroanesthesia. Desflurane when used for a prolonged period has been shown to increase ICP possibly due to increases in cerebrospinal fluid production. The use of nitrous oxide (N_2O) in neuroanesthesia is becoming rare due

to its potent vasodilatory effect resulting in an increase in CBF. It also increases $CMRO_2$, therefore causing a clinically significant rise in ICP. Nitrous oxide should be avoided in patients with severely reduced intracranial compliance, in patients at risk of developing venous air embolism and pneumocephalus, during ventricular drainage and in the presence of air in the ventricles.

Other Drugs Affecting the Brain

Dexmedetomidine

Dexmedetomidine, a highly selective centrally acting α_2-adrenoceptor agonist is increasingly used as a sedative agent in intensive care unit (ICU) and is currently approved by Food and Drug Administration for short-term sedation of less than 24 h, though many studies have reported its safe use for longer duration. It has neuroprotective effects and is considered the near-ideal sedative agent in the ICU, due to its ability to maintain a patient's cooperation with minimal effect on respiratory function. Many studies had been carried out to evaluate its effect on CBF, $CMRO_2$ and ICP. Dexmedetomidine was found to have no effect on ICP. It had been shown to cause a dose-related reduction in both CBF and $CMRO_2$ in healthy subjects. However, these study results do not confirm that dexmedetomidine will not cause adverse effects on the CBF to CMR ratio in patients with cerebral pathology. Large randomized trials are still required to assess its safety in patients with neurologic diseases.

Magnesium Sulfate

This agent, commonly used in the management of eclampsia in obstetrics, is increasingly being used in neuroanesthesia due to its neuronal membrane stabilizing effect that may prevent seizure occurrence. There is evidence to show that the outcome is improved when it is used in patients with SAH. The postulated mechanism is that it lowers the intracellular smooth muscle calcium levels causing cerebral vasodilation.

Opioids

Opioids are commonly used in combination with sedatives or hypnotic agents to provide analgesia in patients undergoing neurosurgery and in patients who require invasive mechanical ventilation in the neurocritical care unit. They have minimal effects on CBF and $CMRO_2$, and carbon dioxide reactivity is preserved at standard clinical doses. However, if hypoventilation occurs and $PaCO_2$ is raised secondary to opioid use, cerebral vasodilation ensues which later results in increased CBF, CBV and ICP.

Drugs Used to Treat Cerebral Edema

Mannitol

This is an osmotic diuretic widely used to treat patients with cerebral edema irrespective of its etiology. Its use is supported by the Brain Trauma Foundation for the management of raised ICP after traumatic brain injury (TBI). There are two mechanisms involved. The first one occurs immediately after a bolus administration through plasma expansion, which decreases blood viscosity resulting in improved cerebral microvascular flow and consequently oxygen delivery to the brain. The second mechanism is due to its osmotic effect in which an osmotic gradient is established between the brain cells and plasma, causing water to be drawn out from the cells thereby reducing cerebral edema. Other than these two mechanisms, mannitol also acts as a free-radical scavenger. It decreases the harmful effect of free radicals during ischemia-reperfusion injury.

Hypertonic Saline

Hypertonic saline is an alternative to mannitol. There is some evidence that it has a more favorable effect compared to mannitol on mortality after TBI but larger trials are needed to prove this effect. Hypertonic saline encourages water to move out of brain cells into intravascular space, reducing cerebral swelling and ICP. Three percent saline can be given as continuous infusion or higher concentration solution is administered as bolus. The patient's volume status and plasma sodium concentration should be closely monitored.

Drugs Affecting CSF Production and Absorption

While these drugs do have an effect on CSF production and absorption, they are not used clinically in the management of brain injury. Certain drugs, particularly the volatile anesthetics, alter the mechanics of CSF production and absorption. For instance, isoflurane decreases the production and increases reabsorption of CSF. Sevoflurane causes a decreased in production but does not affect reabsorption. Prolonged administration of desflurane has been shown to cause significant rise in ICP, which is likely to be caused by increased CSF production. All opioids at low doses produce small increase in CSF absorption.

If the production of CSF is increased without any change in absorption, the increased volume of CSF within the skull will result in a rise in ICP. There are agents that are still in the experimental stage that can affect CSF outflow mechanics and potentially be utilized to reduce raised intracranial pressure.

Key Concepts

- Knowledge of cerebral physiology and its alteration by drugs is vital for caregivers managing patients with cerebral pathology.
- In patients with raised ICP, CBF needs to be maintained to meet metabolic demand and prevent secondary brain damage.
- Cerebral pathology can be managed by decreasing $CMRO_2$, maintaining adequate cerebral blood flow and oxygenation, and decreasing ICP.

Summary

Integrity of the brain is essential for meaningful survival. Therefore, it is crucial for all caregivers to understand the physiological process in the brain in a healthy person and its changes in disease states in order to provide appropriate and timely care. Early pharmacological modulation of abnormal physiological parameters is vital to ensure adequate blood flow to the brain so that oxygen and energy needs are met. While pharmacological measures are important in the management of brain pathology, other therapy including ventilation and oxygenation of the brain injured patient, and control of ICP via drainage of CSF play a big role. The ultimate aim is to prevent neuronal dysfunction and irreversible brain damage.

Further Reading

1. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007;24 Suppl 1:S1–106.
2. Brunton L, Blumenthal D, Buxton I, Parker K, editors. Goodman & Gilman manual of pharmacology and therapeutics. 11th ed. New York: McGraw-Hill; 2008.
3. Fitch W. Physiology of the cerebral circulation. Best Pract Res Clin Anaesthesiol. 1999;13(4):487–98.
4. Glasby MA, Myles LM. Applied physiology of the CNS. Surgery. 2005;23(1):7–12.
5. Hutchinson PJ, Kirkpatrick PJ. Decompressive craniectomy in head injury. Curr Opin Crit Care. 2004;10:101–4.
6. Jantzen JP. Prevention and treatment of intracranial hypertension. Best Pract Res Clin Anaesthesiol. 2007;21(4):517–38.
7. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's pharmacology. 7th ed. Edinburgh: Churchill Livingstone; 2012.