Chapter 11
Perioperative Pharmacotherapy in Neurosurgery: Risk Assessment and Planning

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There is a multiplicity of drugs that can be used during the perioperative period. Each has indications and adverse reactions that must be appreciated.

Inhaled Anesthetics

Overview

These drugs are widely used as fundamental components of general anesthesia.

Implications for the Neurosurgical Patient

In addition to their marked cerebrovascular effects, inhaled anesthetics produce important hemodynamic and respiratory changes in a dose-dependent manner that can have a significant impact on the neurologic patient.

Concerns and Risks

All inhalational anesthetics are potent cerebral vasodilators in a dose-dependent fashion; therefore, they have the potential to increase intracranial pressure (ICP).

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Halothane is the most powerful cerebral vasodilator; however, currently it has limited use. It produces an increase in cerebral blood flow in association with a decrease in cerebrovascular resistance that can result in significant increases in ICP. Controlled hyperventilation can help to limit this effect.

Isoflurane, sevoflurane, and desflurane produce cerebral vasodilation and an increase in ICP, but the effects are clinically significant with doses higher than 1 MAC. Desflurane might produce more vasodilation than the others and has been proposed to be the inhaled agent of choice for brain protection in patients undergoing temporary cerebral artery occlusion during cerebrovascular surgery.

Nitrous oxide has a variable effect from zero to marked cerebral vasodilation and the potential to increase ICP depending on the initial $PaCO_2$ and the presence of adjuvant anesthetic drugs. Experimental evidence suggests that inhaled anesthetics cause neuro-apoptosis in the very young and the brain of the elderly. Nitrous oxide is the only inhaled agent that appears to worsen short-term outcome following transient focal cerebral ischemia.

Key Points

- Inhaled anesthetics as a group cause cerebral vascular dilation and increased ICP in high doses.
- Avoid halothane if possible.
- Use isoflurane, sevoflurane, or desflurane at a concentration ≤ 1 MAC.
- Use nitrous oxide cautiously.

Suggested Reading

Patel MP, Drummond JC. Cerebral physiology and the effects of anesthetic drugs. In: Miller RD, editor. Miller's anesthesia. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2010. p. 305–40.

Pasternak J, McGregor D, Lanier W, et al. Effect of nitrous oxide use on long-term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. Anesthesiology. 2009;110:563–73.

Intravenous Anesthetics

Overview

They are used virtually in every general anesthetic, either only at induction or also during maintenance. These drugs are responsible for the hypnosis, while opioids provide the analgesic component of general anesthesia (balanced anesthesia).

Implications for the Neurosurgical Patient

In general, intravenous anesthetics reduce the cerebral metabolic rate and oxygen consumption, and because they have no vasodilatory effects, both cerebral blood flow and ICP are proportionally reduced.

Concerns and Risks

The optimal anesthetic should maintain normal coupling between cerebral blood flow and metabolism, keep cerebrovascular autoregulation intact, and not increase cerebral blood volume and ICP, and, ideally, (potentially combined with other drugs) provide neuroprotective effects.

Barbiturates and propofol are used during temporary clipping of intracerebral arteries in cerebral vascular surgery (i.e., aneurysm and extra- to intracraneal by pass surgery) because of their allegedly neuroprotective effects in focal ischemia. When barbiturates are used as the primary anesthetic (usually by infusion), emergence may be delayed. In addition, propofol infusion (short- or long-term) infrequently can be associated with impaired free fatty acid utilization and mitochondria activity (propofol infusion syndrome) often presenting as acidosis, cardiac dysrhythmias, and myocardial dysfunction.

Alpha2-adrenoceptor agonists (e.g., dexmedetomidine) are now being used as a component of a balanced anesthesia and for sedation in the ICU. Although dexmedetomidine is associated with an easily managed level of sedation, rapid administration may be associated with hypertension and slow rate infusion with hypotension. In addition, there is the concern that dexmedetomidine might prevent normal cerebral vasodilation during hypoxemia.

Although etomidate is a reasonable choice for the induction of anesthesia in cardiovascularly compromised patients, it does not confer significant neuroprotection. A single dose of etomidate for the induction of anesthesia produces adrenal suppression that can be relevant in trauma and septic patients. As many neurologically impaired patients are receiving high-dose steroids as part of their underlying therapy, the adrenal suppression effects of etomidate might have less clinical significance in these patients. Etomidate during temporary clipping was associated with a reduction in brain oxygenation and should, therefore, be avoided in this context.

Opioids are necessary components for most surgical procedures, to afford the patient with appropriate intra- and postoperative analgesia. Although they inhibit the respiratory drive, the use of short-acting opioids (fentanyl, alfentanil, and remifentanil) is common in neurosurgical patients. Using the right dose and dosing frequency, even opioids with a long duration of action can be used safely (e.g., hydromorphone). The use of opioids and benzodiazepines requires caution, particularly toward the end of surgery, as they will impair respiratory drive leading to significant increments in $PaCO_2$ and ICP.

Table 11.1 shows the effect of different drugs on some important parameters.

Table 11.1 Effect of different intravenous anesthetics on some cerebral physiologic parameters and arterial pressure

	CBF	CMR	ICP	CO_2 reactivity	Arterial pressure
Barbiturate	⇓⇓	⇓⇓	⇓⇓	0	⇓
Propofol	⇓⇓⇓	⇓⇓	⇓	0	⇓⇓
Etomidate	⇓⇓	⇓⇓	⇓⇓	0	0
Benzodiazepines	⇓	⇓	⇓ or 0	⇓⇓	0
Ketamine	⇑	⇑ or 0	⇑	?	⇑
Opioids	0	0	0	⇓	⇓ or 0

CBF, cerebral blood flow; CRM, cerebral metabolic rate; ICP, intracranial pressure; ⇑/⇓, slight increase/reduction; ⇓⇓, significant reduction; ⇓⇓⇓, marked reduction; 0, without significant effect; ?, uncertain effect

Key Points

- Consider intracranial distensibility and hemodynamic parameters to choose the appropriate intravenous anesthetics.
- The use of benzodiazepines and opioids to sedate and treat pain in awake patients with closed head trauma must be done very carefully.

Suggested Reading

Jackson WL. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock?: a critical appraisal. Chest. 2005;127(3):707–9.

Martyn JA. Neuromuscular physiology and pharmacology. In: Miller R, editor. Miller's anesthesia. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2010. p. 341–60.

Reves J, Glass P, et al. Intravenous anesthetics. In: Miller R, editor. Miller's anesthesia. 7th ed. Philadelphia: Elsevier Churchill Livingstone; 2010. p. 719–68.

Neuromuscular Blocking Drugs

Overview

Neuromuscular blocking drugs (NMBs) are used to facilitate tracheal intubation, to assure lack of movement during surgery and sometimes to facilitate mechanical ventilation in the ICU.

Implications for the Neurosurgical Patient

NMBs are used in virtually all the neurosurgical patients; however, they have several adverse effects that can be harmful for these patients.

Concerns and Risks

NMBs can be classified into two groups according to their mechanism of action.

(a) *Depolarizing NMBs*: succinylcholine is the only drug of this group in clinical use. Its rapid onset of action makes it particularly useful to obtain a rapid control of the airway. Some of its problems in neurologic patients include:

Transient increase in ICP that might be dangerous when it is already elevated. Adequate depth of anesthesia, normal arterial pressure, and controlled $PaCO_2$ are required to reduce this adverse effect.

Hyperkalemia: a single dose of succinylcholine (1–2 mg/kg) usually increases potassium plasma levels by approximately 0.5–1.0 mEq/L; however, in some patients with severe skeletal muscle trauma, denervation injury with skeletal muscle atrophy, upper motor neuron lesions, paraplegia, spinal cord injury or transection, stroke, and closed head trauma, severe hyperkalemia leading to cardiac arrest has been described. The mechanism for hyperkalemia appears to be linked to the stimulation of extra-junctional receptors which increase on the muscle surface secondary to the above-mentioned diseases.

(b) *Nondepolarizing NMBs*: include pancuronium, vecuronium, rocuronium, atracurium, and several others. With the advent of intraoperative electrophysiologic monitoring, use of nondepolarizing NMBs has become more limited. The use of these drugs is contraindicated during EMG monitoring (e.g., acoustic neuroma surgery and facial nerve monitoring) or motor evoked potentials (e.g., for spine surgery). Great caution must be used when administering nondepolarizing NMBs in patients who have previously experienced a cerebral vascular accident (i.e., ischemic stroke). In addition to the higher risk of hyperkalemia from depolarizing NMBs (see above), these patients are at high risk of being overmedicated with nondepolarizing NMBs, particularly if neuromuscular monitoring is done on the paretic extremity (because of the higher concentration of post-synaptic receptors in that extremity secondary to upregulation).

Residual paralysis secondary to their use is not a real adverse effect but undesired clinical practice and can lead to upper airway obstruction, hypoxemia, and hypercarbia within minutes. In addition, it has been associated with a higher rate of postoperative respiratory complications. To avoid this complication, the routine use of neuromuscular monitoring and careful clinical assessment before extubation is mandatory. Clinical manifestations include respiratory difficulty, problems swallowing secretions, and muscular weakness. Residual paralysis must be rapidly treated with anti-acetylcholinesterases.

Key Points

- Succinylcholine should be used with great caution and only if it cannot be substituted with a non-depolarizing neuromuscular blocking agent.
- Residual paralysis must be ruled out and properly treated before extubation to be sure that the patient is safe while spontaneously breathing.

Suggested Reading

Minton MD, Grosslight K, Stirt JA, et al. Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. Anesthesiology. 1986;65(2):165–9.
Murphy GS, Szokol JW, Marymont JH, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the post anesthesia care unit. Anesthesiology. 2008;109(3):389–98.

Inotropic and Vasoactive Drugs

Overview

The recognition that cerebral hypoperfusion is associated with adverse outcome in acute brain syndromes and during neurosurgery has led to an increase in the use of vasoactive drugs. Thus, some of the inotropes (adrenaline, dopamine, dobutamine, etc.) and vasoactive drugs (phenylephrine and noradrenaline) are extensively used in neurologic patients during surgery and ICU care. In some cases, vasodilators (sodium nitroprusside, nitroglycerin, calcium channel blockers, etc.) are also used.

Implications for the Neurosurgical Patient

Normally inotropic drugs have minimal or no direct effect on cerebral vessels; therefore, their effects on cerebral perfusion pressure (CPP), cerebral blood flow, intracranial volume, and ICP mostly depend on their effects on systemic hemodynamics. In patients with areas of brain with poor or lack of autoregulation (e.g., tumor, ischemia, or trauma), the maintenance of arterial pressure within a very tight range is critical. Sodium nitroprusside and nitroglycerin may worsen neurologic injury. While they do not have direct cerebrovascular vasodilatory effects, the reduction in arterial pressure may lead to vasodilation in areas of preserved autorregulation and, secondarily, to an increase in ICP: This will result in a reduction of CPP.

Concerns and Risks

Aggressive use of vasopressor drugs and fluids to raise arterial pressure can lead to systemic (pulmonary edema, cardiac failure, and myocardial ischemia) and neurologic (brain bleeding and edema) complications.

Intravenous, and to a lesser extent also by oral route, nimodipine as a prophylaxis of cerebral vasospasm after subarachnoid hemorrhage, can result in arterial hypotension. However, this does not contraindicate its use.

Key Points

- Treat and exclude reversible causes of hypotension before using vasopressor drugs to improve CPP.
- Limited experimental and clinical evidence suggests that norepinephrine might be the most appropriate catecholamine to augment cerebral perfusion in traumatic brain injury.
- Recommended therapy for severely elevated arterial pressure after acute stroke include labetalol, nicardipine, and nitroprusside (used with great caution in patients with elevated ICP). Hemodynamic goals are greatly different between hemorrhagic stroke (tight control to prevent rebleeding) and ischemic stroke (permissive hypertension to improve collateral flow).
- Any pharmacologic intervention to reduce elevated arterial pressure in neurologic patients has to be very slowly and should be intensively monitored. With continuous treatment regimes, careful and repeated reassessments are paramount with particular considerations of the treatment effects on CPP.

Suggested Reading

Pfister D, Strebel SP, Steiner LA. Effects of catecholamines on cerebral blood vessels in patients with traumatic brain injury. Eur J Anaesthesiol. 2008;42(Suppl):98–103.

Talbert RL. The challenge of blood pressure management in neurologic emergencies. Pharmacotherapy. 2006;26(8 Pt 2):123S–30S.

Diuretics and Hypertonic Saline

Overview

Diuretics, particularly mannitol and furosemide, and hypertonic saline are used in neurosurgical patients to reduce ICP and/or to obtain intraoperative brain relaxation.

Implications for the Neurosurgical Patient

Adverse effects are predictable and usually dose dependent. Therefore, these drugs can be applied safely to the neurosurgical patient if the clinician treats these known adverse effects in a preemptive fashion.

Concerns and Risks

Hypovolemia: secondary to diuretics can result in hypotension and reduced CPP.

Hypervolemia: secondary to the use of mannitol and/or hypertonic saline. Although this is rather a theoretical problem, it is transient and would only theoretically occur after rapid administration. The consequences of transient hypervolemia would be most significant in patients with a history of congestive heart failure.

Electrolyte disorders: secondary to a high urine output (hyponatremia and hypokalemia) or massive load of crystalloid solutions, particularly hypertonic saline. Mannitol causes sodium diuresis, which should be replaced to prevent hyponatremia. Loop diuretics (e.g., furosemide) cause hypokalemia, hypocalcemia, and hypomagnesaemia, which can cause cardiac arrhythmias and hypotension. When hypertonic saline is used for hyperosmolar treatment, it can produce hypernatremia and hyperchloremic metabolic acidosis. When using hypertonic saline (e.g., as a 3% solution) in the neurosurgical patient, many clinicians limit administration to a serum sodium not higher than 150 mEq/L. Hyperchloremic metabolic acidosis can be prevented by administering the 3% sodium as a 50% mix of chloride and 50% as acetate.

Key Point

- Monitor electrolyte status after a period of high urine output and/or hypertonic saline administration.

Suggested Reading

Rozet I, Tontisirin N, Saipin M, et al. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology. 2007;107:697–704.

White H, Cook D, Venkatesh B. The role of hypertonic saline in neurotrauma. Eur J Anaesthesiol. 2008;42(Suppl):104–9.

Antiemetic Drugs

Overview

Post-craniotomy patients (this excludes transsphenoid hypophysectomy) are at high risk of postoperative nausea and vomiting (PONV). Despite the lack of a documented case of harm caused by retching or vomiting in these patients, an important number of patients undergoing general surgery fear the occurrence of PONV more than postoperative pain. However, the potential risk caused by vomiting, the associated arterial hypertension and high intra-abdominal/intra-thoracic pressure leading to high ICP suggests that avoiding/treating PONV in these patients is warranted.

Implications for the Neurosurgical Patient

Antiemetic drugs (AEDs) for PONV prophylaxis/treatment include several groups of drugs with an excellent safety profile in general surgery patients. However, some agents (e.g., droperidol and haloperidol) are associated with sedation. Droperidol is also an alpha-1 receptor agonist and may be associated with transient hypotension.

Concerns and Risks

Some adverse effects might be more relevant in neurosurgical patients.

Hyperglycemia: It is the most frequent known adverse effect after dexamethasone 8–10 mg IV. Steroid-induced hyperglycemia peaks between 8 and 10 h after IV administration and can exceed 200 mg/dL. Significant hyperglycemia has been demonstrated to impair neurologic outcomes and increases the risks for infection and impair wound healing. The use of dexamethasone for PONV in patients undergoing intracranial surgery should possibly not be considered the first-line therapy.

Sedation: A decrease in level of consciousness can occur secondary to droperidol and haloperidol and is more frequent within the first 6 h after its administration. It is dose-dependent and very uncommon after ≤1 mg IV of these AEDs. However, these drugs should be avoided in patients having craniotomy because the differential diagnosis of decreased level of consciousness may be unnecessarily complicated in the immediate post-craniotomy period.

Extrapyramidal side effects: They can be secondary to droperidol/haloperidol and metoclopramide, usually after higher than recommended doses. Rarely, administration of haloperidol, droperidol, promethazine, and metoclopramide may cause neuroleptic malignant syndrome. In the postoperative period of neurosurgical patient,

this diagnosis must be considered in the presence of rigidity, autonomic dysfunction, hyperthermia, and mental status changes. If unrecognized and improperly treated the outcome could be fatal.

Headache: Occurs in 3–5% of patients given 5-HT(3) antagonists at the usual doses (such us ondansetron and granisetron) and must be taken into consideration for the differential diagnosis of headache in the neurological patient.

Key Points

- Monitor blood glucose levels after dexamethasone administration. Treat hyperglycemia in neurological patients to a goal of 130–180 mg/dL (current recommendations).
- Neurological and surgical causes of sedation, extrapyramidal signs, and headache must be ruled out before assuming that they are secondary to AEDs.

Suggested Reading

Lukins MB, Manninen PH. Hyperglycemia in patients administered dexamethasone for craniotomy. Anesth Analg. 2005;100:1129–33.
The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–9.

Anticonvulsants

Overview

A large number of patients undergoing a craniotomy are under or will be given anticonvulsants during the perioperative period. Possibly the most used are phenytoin, phenobarbital, and carbamazepine. However, benzodiazepines and thiopental can also be used, especially during active seizures.

Implications for the Neurosurgical Patient

Adverse effects are predictable and usually dose dependent. However, it must be remembered that, postoperatively, patients may have reduced protein binding (particularly affecting phenytoin) due to altered albumin and other drug-binding proteins making it imperative to monitor free drug concentrations in the perioperative period.

Concerns and Risks

Hypotension: secondary to almost all these drugs especially when administered quickly by the intravenous route. Hypotension is often accentuated when these drugs are administered during surgery, as they may act synergistically with anesthetic agents having the same cardiovascular effects.

Bradycardia/arrhythmia: phenytoin when injected fast can produce arrhythmia including asystole. This risk is accentuated when the drug is administered during the period of general anesthesia.

Sedation/respiratory depression: secondary to benzodiazepines and barbiturates. Respiratory depression can result in an increased arterial tension of CO_2 and hypoxemia in patients breathing spontaneously and thereby potentially in severe secondary brain injury.

Interaction with neuromuscular blockers (*NMBs*): chronic treatment with phenytoin and carbamazepine is associated with modest increase in acetylcholine receptor numbers, induced liver metabolism and increased release of acute phase reactant proteins that bind the NMDs, all causing reduced duration of neuromuscular blockade.

Key Points

- Administer slowly when active seizures are not currently present. Never inject phenytoin at a rate > 50 mg min^{-1}.
- When barbiturates and benzodiazepines are administered at a fast rate, check hemodynamic and respiratory status frequently until patients recovers; consider admission to the intensive care unit.
- Monitor intraoperative neuromuscular blockade more frequently in patients under treatment with phenytoin and carbamazepine.
- In the presence of severe cutaneous reactions in patients receiving anticonvulsants other than benzodiazepines, consider changing to a different family of drugs.

Suggested Reading

McNamara J. Drugs effective in the therapy of epilepsies. In: Hardman JG, Limbird LE, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill; 2001.