Neuroprotective effects of thiopental, propofol, and etomidate

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In selecting an anesthetic agent to be used for neurosurgical procedures, the anesthesia provider must consider the agent’s effects on intracranial pressure (ICP), cerebral blood flow (CBF), and cerebral metabolic rate of oxygen consumption (CMRO₂). The anesthetic of choice for neurosurgical procedures for many decades has been thiopental. It meets the strict requirements for neurosurgical procedures because it protects the brain from ischemia and herniation by lowering ICP through decreases in CBF and CMRO₂. However, new drugs, including etomidate and propofol, have been introduced that offer anesthesia providers comparable neuroprotective actions plus other positive attributes. The purpose of this course is to review current and benchmark literature on thiopental, propofol, and etomidate to compare researchers’ reports of the effects on ICP, CMRO₂, and CBF.

Literature was gathered using computer assistance to search PubMed, the Cumulative Index of Nursing and Allied Health Literature, and the World Wide Web. The literature showed that all 3 anesthetic agents provide favorable neurological protection. Each drug has some undesirable side effects. Knowledge of these side effects and the patient’s medical and surgical history can help CRNAs determine the most suitable anesthetic in specific situations.

Key words: Anesthetic neuroprotection, thiopental, propofol, etomidate.

Objectives
At the completion of the course, the reader should be able to:
1. Describe the relationships among intracranial pressure (ICP), cerebral metabolic rate of oxygen consumption (CMRO₂), cerebral blood flow (CBF), and the brain’s autoregulation.
2. Describe the effects of thiopental, etomidate, and propofol on intracranial pressure.
3. Determine how the oxygen requirements for the brain are changed by each of the aforementioned anesthetic agents.
4. Differentiate among the effects of the 3 agents on CBF.
5. Determine whether specific side effects of any of the anesthetics make it a more or less desirable choice for a given patient situation.

Introduction
Neurosurgical patients and those with neurological disorders undergoing nonneurological surgery present challenges for nurse anesthetists. CRNAs must take into account the pharmacodynamics and pharmacokinetics of each anesthetic agent. The appropriate anesthetic plan for these patients requires knowledge of the effects of each anesthetic on ICP, CBF, and CMRO₂.

The anesthetic plan of care can be divided into 3 phases: induction, maintenance, and postoperative care. Each phase presents its own set of requirements and possible complications to consider. The induction phase requires an adequate level of anesthesia to attenuate the sympathetic response to tracheal intubation and patient positioning. The second phase of anesthesia involves maintaining adequate cerebral perfusion pressures throughout the procedure while minimizing any fluctuations in ICP, CBF, and CMRO₂. After the procedure, the patient remains intubated or can be extubated based on the patient’s condition and the neurosurgeon’s request. Early extubation provides
the neurosurgeon with the ability to quickly assess the neurological status of the patient. However, if the patient remains intubated following the procedure, the accentuated sympathetic responses of extubation, including coughing and hypoventilation, can be avoided. In designing an anesthetic plan for a patient with underlying neurological dysfunction, CRNAs must account for all of the aforementioned factors for each anesthetic agent during each phase of anesthesia.

Thiopental (Pentothal) has been the anesthesia provider’s induction agent of choice for neurosurgical procedures for more than 70 years. Because thiopental has been used so widely over the years, many anesthesia providers consider it the “gold standard” against which all newer induction agents should be judged.1 Many studies have shown that thiopental protects the brain by decreasing CBF, CMRO₂, and ICP. The fact that it decreases CBF less than CMRO₂ makes it beneficial for use in patients with cerebral swelling. However, thiopental can cause bronchospasm, and large doses can cause decreases in arterial blood pressure, stroke volume, and cardiac output, all of which can be deleterious to neurosurgical patients.¹

During the last 20 years, 2 other intravenous anesthetics have been introduced that seem to have neuroprotective capabilities similar to those of thiopental. Both are nonbarbiturate hypnotics that have grown in popularity among anesthesia providers.

Etomidate obtained its recognition as a neuroprotective agent through several research studies conducted in the late 1970s. In addition to its neuroprotective capabilities, etomidate has a major advantage over other agents in that it causes minimal cardiovascular and respiratory depressant effects.¹ This makes it desirable for use in patients with coexisting diseases such as hypertension, congestive heart failure, or a history of myocardial infarction.

A newer agent, propofol, has become a drug of choice for many outpatient procedures due to its rapid onset and short half-life—characteristics that make it well suited for neuroanesthesia.² After its use, patients feel better during the postoperative period compared with other intravenous anesthetics. It seems to prevent and relieve nausea and vomiting, and patients are able to ambulate sooner. It does, however, cause a marked decrease in systemic blood pressure during induction and has greater negative inotropic effects on the heart than etomidate and thiopental.¹

Intracranial pressure

The intracranial compartment is enclosed by a bony structure. Its contents consist of brain tissue, blood, and cerebrospinal fluid. Each component directly affects the other in that if the volume of 1 component increases, the other 2 components must compensate by decreasing in volume. The sum of the pressures intracranially equals the ICP. An increase in ICP greater than what the central nervous system can tolerate results in tissue hypoxia and the possibility of brainstem herniation into the foramen magnum, a condition incompatible with life. The ICP can be affected by anesthetics that increase or decrease CBF, CMRO₂, or cerebrospinal fluid drainage or reabsorption.

In the literature reviewed, thiopental showed a tendency to significantly decrease ICP. Nordstrom et al³ showed that patients being maintained in a coma state whose cerebral vasoreactivity (CVR) was maintained had a substantial decrease in ICP. This decrease did not hold true for those with impaired CVR. Slogoff et al,⁴ using high doses of thiopental, concluded that the agent significantly reduced the incidence of neurological deficits in patients undergoing coronary artery bypass surgery. However, these researchers also showed a correlation between thiopental and a long recovery period and an increased need for inotropic and chronotropic drugs.

Etomidate proved to be an appropriate drug for patients with compromised ICP. In a study of patients with intracranial lesions, the authors concluded that 0.2 mg/kg of etomidate can significantly decrease ICP.⁵ Patients who had sustained severe head injuries were given 2 mg/kg of propofol, which provided a significant decrease in ICP after 30 seconds and even further decreases after 1 and 2 minutes.⁶ In patients undergoing elective intracranial surgery, 1.5 mg/kg of propofol was used for induction. Two minutes after administration of propofol alone, the ICP decreased by 32%, but it returned to baseline values by 3 minutes.⁷ Pinaud et al⁸ conducted a study in which propofol was administered to patients with closed head injuries who were undergoing orthopedic surgery. Induction with propofol at 2 mg/kg was followed by a continuous infusion at 150 µg/kg per minute. The ICP decreased within 5 minutes of the initiation of the propofol and returned to preinduction values 15 minutes after propofol was discontinued.

According to the literature, all 3 anesthetics significantly decrease ICP, but thiopental was found to decrease ICP only if CVR remained intact.⁸ Researchers also found that greater inotropic and chronotropic support was needed following the use of thiopental. Etomidate and propofol, on the other hand, decreased ICP without causing hemodynamic instability. Propofol demonstrated a more transient effect on ICP, but, as long as propofol was infusing, the ICP remained decreased.
Cerebral metabolic rate of oxygen consumption

The brain requires an uninterrupted, steady blood flow to meet its energy needs. The brain constitutes only 2% of the body's weight, but it is supplied with 14% of the body's resting cardiac output. It removes 10% of the blood's available glucose in one pass. It also consumes an average of 140 µmol of oxygen per 100 g of brain tissue each minute.\(^9\)

The CMRO\(_2\) is a reflection of the oxygen requirements for the brain. Anesthetics have been shown to decrease neuronal activity and, thus, decrease the demand for oxygen by the brain. When the CMRO\(_2\) decreases, a parallel decrease occurs in CBF, with a resultant decrease in ICP. This information can be used advantageously for the patient with underlying neurological complications. It is important to note the effects of thiopental, etomidate, and propofol on CMRO\(_2\) to determine whether they can be administered safely during neurosurgical procedures.

Several animal studies revealed that thiopental provided neuroprotection in cases of ischemia or hypotension. Experimental animals showed less morbidity and mortality than did control animals.\(^{10,11}\) Animals given thiopental required less energy for maintenance of cerebral function, showing that thiopental reduced CMRO\(_2\).

Nordstrom et al\(^3\) explored the effects of barbiturate coma on the CMRO\(_2\) of people with severe brain lesions. In these studies, thiopental initiation was followed by a continuous infusion until the patient's monitored ICP was decreased and maintained at or below 20 mm Hg for at least 12 hours or until the treatment was considered ineffective. CBF and CVR also were measured. Patients with preserved CVR showed a decrease in CMRO\(_2\) of 28% and an accompanying decrease in CBF of 29%. Patients with impaired CVR had no changes in CMRO\(_2\), CBF, or ICP.

In research with dogs as subjects,\(^{12}\) etomidate produced dose-related changes in electroencephalograms (EEGs), demonstrating that its effects on neuronal function were similar to those of thiopental. Continued administration of etomidate in increasing doses was associated with a progressive reduction in CMRO\(_2\). Once an isoelectric EEG indicated that neuronal function had been suppressed, there was no further effect on CMRO\(_2\). This occurred around 91 minutes after the start of the etomidate, at which time the CMRO\(_2\) stabilized at approximately 48% of that of the controls. The minimum CBF value was achieved around 45 minutes before the CMRO\(_2\) stabilized, but despite this time difference, oxygen delivery to the brain cells appeared to be adequate. During the experiments, etomidate showed minimal effects on hemo-

dynamic variables (cardiac function, heart rate, myocardial contractility, blood pressure, and myocardial oxygen consumption).\(^1\) These findings support the use of etomidate in patients in whom decreases in CMRO\(_2\) would be beneficial. Deaths attributed to central nervous system complications during cardiac surgeries rose from 7.2% in the 1970s to 20% or more in the 1990s. This was thought to be related to the increasing number of older patients with a risk for neurologic dysfunction. Hypothermia and thiopental were used for protection of the central nervous system, but they did not prove adequate, so study was undertaken to investigate the cerebral protective effects of propofol.\(^{13}\) This study examined the effects of propofol on cerebral physiology at burst suppression levels during the normothermic and hypothermic phases of cardiopulmonary bypass. Dose levels of propofol necessary to reach burst suppression on the EEG decreased when hypothermia was instituted. Propofol produced statistically significant reductions in CMRO\(_2\) (a 56% reduction during the normothermic phase and an even greater decrease during hypothermia). These decreases were greater than those produced by thiopental. Propofol also caused less cerebral vasoconstriction than thiopental and reduced CBF less than did thiopental, leading the researchers to conclude that the neuroprotective effects of propofol were achieved by a different mechanism and to postulate that propofol might be more desirable in relation to the cerebral oxygen supply/demand ratio. With a reduction in the amount of blood flow to the brain, it was hypothesized that there could be a concomitant reduction in cerebral exposure to emboli that might be released during cardiopulmonary bypass surgery, especially during clamp placement, clamp removal, and resumption of cardiac ejection.\(^{15}\)

Thiopental, etomidate, and propofol decrease cellular function and, thus, decrease CMRO\(_2\), which reduces cellular function and requirements for critical energy sources. This means that CBF can slow and the risk for increased ICP can be reduced. Although propofol decreases CMRO\(_2\) to a greater extent than does etomidate or thiopental, all 3 anesthetic agents decrease CMRO\(_2\) sufficiently to provide favorable cerebral protection.

Cerebral blood flow

As previously mentioned, the brain receives a large proportion of cardiac output relative to its size. This is necessary because of the high metabolic rate of the cerebral tissue.\(^9,14\) The most metabolically active organ, the heart, has a coronary blood flow of 60 to 100 mL/100 g of heart tissue. The CBF in a healthy, conscious individual varies widely among the regions

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of the brain, depending on the functional activity at the time, such as listening, thinking, or directing movement. However, the overall average CBF is 50 mL/100 g of brain tissue per minute. In contrast with most other tissues, the brain does not have sufficient stores of oxygen and glucose to support its needs. Low storage of energy sources and a relatively high metabolic rate can lead to serious deprivation for the brain cells should blood flow be compromised.

Autoregulation is the brain's mechanism for controlling CBF in the face of a constantly changing cerebral perfusion pressure. The physiological system can maintain a constant CBF within a cerebral perfusion pressure range of 50 to 150 mm Hg. Cerebral autoregulation, however, is a sensitive mechanism that can be impaired by general anesthesia. The ability of the anesthesia provider to decrease the CBF safely during surgical procedures is essential for preventing cerebral tissue hypoxia and subsequent irreversible neuronal injury or death.

When anesthetics decrease neuronal activity, they also produce cerebral metabolic depression. For most anesthetic agents, this decrease continues until the EEG shows an absence of neuronal function. As long as neuronal function is present, anesthesia providers can affect neuronal energy requirements through control of the anesthetic agent. Thiopental was one of the first anesthetics used to decrease CBF in this manner.

The CBF was evaluated during the administration of etomidate to dogs. The infusion was increased at 20-minute intervals. CBF decreased sharply at the initiation of the etomidate infusion, and within 7 minutes it was half the value of the control group's CBF. The CBF reached its minimum value at 45 minutes of infusion. The CMRO₂, however, continued to decrease progressively over time until it reached its minimum value when an isoelectric EEG indicated cessation of neuronal function at 91 minutes. Despite continued administration of etomidate in increasing doses, CBF and CMRO₂ stabilized at their minimum values. The brains of the experimental animals showed no signs of cerebral ischemia, nor were there any significant changes in systemic variables. There was an association between decreases in CBF and increases in cerebral vascular resistance. The researchers concluded that etomidate is a potent cerebral vasoconstrictor but that this effect is not secondary to its effect on cerebral metabolism. This conclusion disagreed with that of Renou et al. who earlier studied patients undergoing diagnostic carotid angiography and reported that there was a coupling between CBF and CMRO₂. Mild et al. determined that the discrepancy might be because Renou et al. used a single dose of etomidate and had fewer points on the response curve. Both groups concurred that etomidate was a cerebral metabolic depressant and a potent cerebral vasoconstrictor and that it reduced CBF. These findings, along with its ability to maintain hemodynamic stability, make etomidate a good choice for general anesthesia during neurosurgical procedures (but may make it questionable for inducing coma to reduce cellular function in stroke because higher blood flow may allow for more free oxygen radicals that could lead to more cellular damage).

Propofol was shown to be a safe choice for anesthesia when considering ICP and CMRO₂. Several different studies revealed that propofol also decreased CBF safely. One such study compared the effects of propofol and volatile anesthetics and concluded that propofol decreased CBF to a greater extent than did the inhaled agents while still preserving cerebral autoregulation. The inhalants ablated the dynamic and static rates of regulation. Another study with patients undergoing spinal surgery showed a CBF reduction of 28% when propofol was initiated after volatile anesthetics and used as a continuous infusion. It should be noted that the initial induction was accomplished with thiopental. This may have accounted for the failure of propofol to achieve the same percentage decreases as previously found.

In cases of stroke, the goal of the anesthesia provider is to produce a coma for the purpose of reducing cellular functioning. This reduction allows time for free oxygen radicals (thought to cause cellular damage) to be scavenged and removed by endogenous antioxidants. The highest concentration of these radicals occurs during reperfusion after the initial vasoconstriction. Unlike other anesthetics, propofol has shown antioxidant activity. The effects of propofol after stroke were examined by Bayona et al. When propofol was initiated within 2 hours of an induced infarction and continuously maintained for an additional 3 hours, it produced a reduced infarct volume compared with the infarct volume of control subjects whose comas were maintained only with the intralipid vehicle. In addition, the propofol-treated animals showed functional improvement between 14 and 21 days (ability to acquire food pellets), whereas the control subjects showed no functional improvement at day 21. Infarct size, however, was about the same for both groups at 21 days, leading to questions about cells that were protected from destruction by early propofol treatment and new cell regeneration that might have been seen in both groups had the experiment continued for a longer time,ie, was coma treatment necessary or effective over time?

For thiopental and propofol, the reduction in CBF was found to be directly related to the reduction in cerebral activity as detected by a decrease in CMRO₂. Etomidate, on the other hand, showed no further
decrease in CBF after it reached its maximal decrease, despite decreases in CMRO₂. It also provided greater hemodynamic stability when compared with thiopental or propofol. Although etomidate may be useful as an induction agent and during cardiovascular surgery in which there is little risk of cerebral ischemia, thiopental or, more likely, propofol may be preferred when a cerebral protective coma state is desired.

Side effects
The anesthesia provider must determine which anesthetic would be most beneficial while taking into account its side effects. Thiopental has the benefit of being the most cost-effective of the 3 anesthetics. However, thiopental has a half-life of approximately 11 to 14 hours.¹ The long half-life makes early postoperative assessment of the neurologic status of the patient difficult.

Both thiopental and propofol have been shown to produce hemodynamic instability that can result in decreased cerebral perfusion pressures.⁸¹⁴ The depressant effects of propofol on respiration (short periods of apnea) need to be considered, especially during initiation and withdrawal of mechanical ventilation.¹⁹

Because the vehicle for propofol is a lipid, several side effects are associated with its use. In addition to causing venous irritation on injection, it is capable of supporting bacterial growth. To prevent infection, the propofol vial and the intravenous tubing need to be discarded as frequently as every 6 hours and no longer than 12 hours after initiation of an infusion. The necessity of throwing unused drug away adds significantly to its already high cost. Patients also tend to develop a tolerance to propofol infusion if it is continued past 7 days, but a need for higher doses increases lipid levels. High lipid levels may warrant discontinuing or decreasing propofol and adding other sedatives.¹⁹ In any case, propofol infusion at rates higher than 5 mg/kg per hour should be discouraged for long-term sedation because of a phenomenon known as propofol infusion syndrome, which leads to deaths similar to those found in children receiving propofol (myocardial failure, metabolic acidosis, and rhabdomyolysis).²⁰

Etomidate is known to cause irritation to the veins on induction and a period of myoclonus, which are similar to the side effects of propofol. Of more importance is the effect of etomidate on cortisol suppression. Etomidate is a selective inhibitor of the enzyme that converts deoxycortisol to cortisol, producing a partial adrenocortical insufficiency. This phenomenon was discovered when mortality rate of multitrauma patients, as assessed in the early postoperative period. Propofol also decreases analgesic and postoperative antiemetic requirements and allows for earlier ambulation than do other anesthetics. A study of cardiopulmonary bypass surgery reported that propofol lowered

Summary
Thiopental, etomidate, and propofol are excellent agents for neuroanesthesia. They are all intravenous anesthetics that do not require specialized equipment for their delivery or cleanup. Their onset of anesthetic action is faster than inhaled agents, and their rates of recovery make them acceptable for outpatient procedures.³ All 3 anesthetics can be administered safely to patients who have underlying neurological complications, but the duration for which they should be administered and the length of time to recovery differ. The comparisons presented in this article can help anesthesia providers make an informed decision about which agent is most appropriate in a given clinical situation.
CMRO₂ to a greater degree than did thiopental. This would lead one to assume that CBF could be slowed, putting less strain on the cardiovascular system.

Recently, propofol, unlike other anesthetics, was shown to produce direct antioxidant activity, which could make it an excellent agent to combat ischemia following stroke. To be effective, it needs to be continued during the time of reperfusion of the ischemic area—the time when ischemic brain damage is more likely to be exacerbated by generation of oxygen free radicals. Caution, however, is recommended in expecting long-term neuroprotection from any anesthetic agent that is administered for only a short time before or after an ischemic episode.

Anecdotal information is circulating about adverse reactions between propofol and the statins, but reports of research on this topic are not available.

Research has shown that each anesthetic is similar in its neuroprotective capabilities for ICP, CBF, and CMRO₂ (Table). Therefore, anesthesia providers must take into account other characteristics and side effects of each agent and determine, based on the history and condition of the patient, which anesthetic would be the most beneficial.

REFERENCES

AUTHORS
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