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Neurosurgical anesthesia
Does the choice of anesthetic agents matter?

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INTRODUCTION

The anesthetic management of neurosurgical patients is, by necessity, based upon our understanding of the physiology and pathophysiology of the central nervous system (CNS) and the effect of anesthetic agents on the CNS. Consequently, a great deal of investigative effort has been expended to elucidate the influence of anesthetics on CNS physiology and pathophysiology. The current practice of neuroanesthesia is based upon findings of these investigations. However, it should be noted that most studies in this field have been conducted in laboratory animals and the applicability of the findings to the human patient is debatable at best. A great deal of emphasis has been placed on the minor differences in anesthetic induced changes in cerebral blood flow (CBF), cerebral metabolic rate (CMR) and intracranial pressure (ICP) that have been consistently demonstrated in a variety of studies. Is this emphasis justified? It is not surprising that, in the absence of controlled studies which demonstrate the superiority of one technique over another, interpretations of the available data differ and that opinions on the optimal approach to the neurosurgical patient also differ. A more important question to the practicing anesthesiologist is not whether the minor differences in CNS physiology induced by anesthetics are relevant to *all* neurosurgical patients but the *identification of clinical situations in which anesthetic effects might be significant*.

In the present discussion, a brief review of the cerebrovascular effects of anesthetic agents will be presented. Thereafter, situations in which the anesthetic selection has been suggested to be relevant will be addressed:

1) Moderate to severe intracranial hypertension
2) Inadequate brain relaxation during surgery
3) Evoked potential monitoring
4) Intraoperative electrocorticography
5) Cerebral protection

CNS EFFECTS OF ANESTHETIC AGENTS

It is now generally accepted that N_2O is a cerebral vasodilator and can increase CBF when administered alone. This vasodilation can result in an increase in ICP. In addition, N_2O can also increase CMR to a small extent. The simultaneous administration of intravenous anesthetics (barbiturates, propofol, benzodiazepines, narcotics) can substantially reduce this increase in CBF and CMR. The behavior of a combination of volatile agents and N_2O is quite different. When administered in low doses, volatile agents can reduce CBF and CMR. The addition of N_2O to low dose volatile agent anesthesia increases both CBF and CMR. This N_2O mediated vasodilation can be greater when higher doses of volatile agents are administered.

Volatile agents uniformly suppress CMR. At doses of 1.5 – 2.0 MAC, the commonly used agents isoflurane, desflurane and sevoflurane all produce burst suppression of the EEG. At burst suppression, CMR is reduced by 50-60%. Volatile agents are also vasodilators. Their effect on CBF is biphasic. At doses of about 0.5 MAC, the suppression in CMR balances the vasodilatory effects and CBF does not change significantly. In doses greater than 1.0 MAC, the vasodilatory effect predominates and CBF increases. The addition of N_2O to volatile anesthetic anesthesia will in-

crease CBF and CMR. This increase in CBF may not necessarily result in an increase in ICP. The effect of volatile agents on cerebral blood volume (CBV) parallel the CBF changes but are of a significantly lesser magnitude.

Intravenous hypnotic agents, with the exception of ketamine, all decrease CMR and CBF substantially. In appropriate doses, barbiturates, propofol and etomidate produce burst suppression of the EEG. Ketamine's effect on CBF and CMR are regionally specific; in the limbic structures, CBF and CMR increase whereas within the cortex, reductions in CBF and CMR occur.

1) MODERATE TO SEVERE INTRACRANIAL HYPERTENSION

Patients with intracranial hypertension (ICH) have symptoms of headache, nausea, vomiting and visual disturbance. Patients with severe ICH also have a reduced level of consciousness. CT scans demonstrate mass lesions, ventricular effacement, midline shifts of the brain and full basal cisterns. The brain's capacity to accommodate increases in CBV is exhausted and even slight increases in intracranial volume can result in dramatic increases in ICP. In patients with acute increases in ICP (for example, with traumatic brain injury, epidural and subdural hematomas), the effect of an increase in CBV on ICP is even greater. It is in these patients that the choice of anesthetic agents must be considered carefully.

Agents that produce vasodilation can increase CBF and more importantly, CBV. The potential for a further increase in ICP is therefore apparent. Minor increases in ICP can be readily treated by modest hyperventilation and the use of diuretics. Consequently, for the majority of patients, it is unlikely that anesthetic induced increases in ICP will be substantial enough to compromise the brain. For example, in patients with intracranial tumors, there were no differences in outcome in patients anesthetized with propofol-fentanyl, isoflurane-nitrous oxide or fentanyl-nitrous oxide[1]. Nontheless, other studies have shown that dural tension is higher with isoflurane-fentanyl and sevoflurane-fentanyl anesthesia in comparison to propofol-fentanyl anesthesia[2]. In patients in whom the ability of the brain to compensate for further increases in CBV is exhausted, a technique that reduces CMR, CBV and ICP *may* be preferable. In such patients, it is the author's practice to avoid nitrous oxide and volatile agents until such time as the dura is opened. An anesthetic technique based on the infusion of propofol and narcotics may be a more prudent approch in so far as the reserve of the brain to compensate for increases in CBV is not encroached upon and may in fact be increased (reduction in CBV). Volatile agents may be introduced once the cranium has been opened and the dura has been reflected; observation of the brain and the surgical conditions can then dictate the anesthetic regimen.

A similar logic may apply to the management of the acutely head injured patient. Compensatory mechanisms are inadequate to offset the rapid increase in intracranial volume and ICP. In such patients, brain distortion and herniation can compromise regional brain perfusion, rendering the brain ischemic. Moreover, experimental data have shown that hyperventilation, which is often employed to minimize or counteract volatile agent induced vasodilation, can be ineffective in doing so with acute head injury[3]. A cogent argument can therefore be made that one should avoid nitrous oxide and volatile agents in the anesthetic management.

"TIGHT BRAIN" DURING SURGERY

Adequate brain relaxation facilitates neurosurgery and reduces the need for excessive brain retraction. Although uncommon, brain swelling can occur intraoperatively during surgery. This is most commonly seen during AVM surgery but it can occur during tumor surgery as well. The etiology of brain swelling is not clear. Clearly, engorgement of the brain with blood plays a significant role. When brain swelling does occur, the brain is placed at risk for ischemic injury. In addition, brain swelling interferes with surgery and on occasion, can prevent closure of the dura. This represents an urgent problem that demands the attention of the anesthesiologist and the neurosurgeon. The approach to this difficult problem is reasonably well established and the following maneurvers may be instituted:

- Check ventilation. Moderate hypocapnia (target $PaCO_2$ 25-30 mmHg) will produce cerebral vasoconstriction and the consequent reduction in brain bulk. Measurement of end-tidal CO_2 tension is occasionally misleading. Arterial blood gas analysis should be utilized judiciously to confirm hypocarbia.
- Ensure normal oxygenation.
- Control blood pressure. Target is normotension (within 10% of baseline blood pressure).
- Ensure adequate venous drainage from the brain. Neck torsion or the placement of endotracheal tube ties around the neck can impede venous drainage from the brain.
- Head elevation (30° optimum)
- Check intrathoracic pressure. Rule out pneumothorax (especially if central line has been placed).
- Maintain adequate neuromuscular relaxation.
- Administer mannitol.

If these measures are not adequate, then consideration should be given to the potential deleterious effect of anesthetic agents. In particular, attention should be focused on

those agents that can increase brain bulk by producing cerebral vasodilation. The manipulation of anesthetic administration can effect dramatic reductions in brain bulk:

- Make sure that the concentration of volatile agent is less than 0.5 MAC
- Discontinue the administration of N_2O
- Discontinue the administration of volatile anesthetics
- Switch to an intravenous anesthetic technique. A combination of propofol and narcotic infusion is ideal.
- If the brain swelling does not abate, then the probability that the patient will have protracted intracranial hypertension in the post-operative period is high. In that event, barbiturates (pentobarbital) may be administered until either the swelling is reduced or until burst suppression of the EEG is attained. On rare occasions, the surgeons may elect to amputate brain or to close the scalp without replacing the bone flap.

2) INADEQUATE SIGNAL QUALITY DURING EVOKED POTENTIAL MONITORING

Somatosensory evoked potentials

All volatile agents attenuate evoked potentials in a dose related manner (see an excellent review by Banoub et al)[4]. Somatosensory evoked potential (SSEP) amplitude can be attenuated at 1.0 MAC concentrations and can be abolished with higher concentrations. Simultaneously, a dose dependent increase is latency is also observed. The newer volatile agents sevoflurane and desflurane appear to depress the amplitude of the SSEP to a lesser extent and their use may permit the delivery of a higher concentration (~1 – 1.5 MAC)[5]. Auditory evoked potentials are relatively robust but even their waveforms will be affected at volatile anesthetic concentrations that exceed 1.5 MAC. N_2O can also reduce the amplitude of the SSEP[6]. Intravenous agents, on the other hand, have a modest impact on evoked potentials; in fact, evoked potentials can be detected even with doses of barbiturates that produce burst suppression of the EEG.

Given that anesthetic agents suppress EPs, the choice of anesthetic agents for the maintenance of anesthesia becomes an important consideration. Although volatile agents and N_2O suppress EPs, stable and robust EP recording can be obtained provided the concentration of the volatile agent is kept to 0.5 MAC or less and the nitrous oxide concentration is maintained in 50-60% range. Without N_2O, the volatile anesthetic concentration can be increased to about 1 MAC. Opiate infusion in addition will provide, in most circumstances, stable anesthetic conditions that permit EP monitoring. If the quality of the signals is not adequate, then the anesthetic technique has to be modified. The technique that results in a very good signal is a total intravenous anesthetic technique. The combination of propofol and a narcotic infusion results in excellent signals in most patients[7]. In addition, the variability in the amplitude of the evoked potential is reduced by this technique in comparison to a N_2O -volatile agent-narcotic technique. This is an important consideraton in those patients with CNS abnormalities in whom the EP is already compromised by the primary disease. If the signal does not improve, then it is highly unlikely that the cause of the problem is the anesthetic.

Etomidate is unique among anesthetic agents in that it actually increases the amplitude of somatosensory evoked potentials. Clinicians often administer etomidate by infusion to improve the quality of the recording. However, it is difficult to determine what exactly an improvement in the signal that is induced by etomidate means to the transmission of the signal from the peripheral nerve to the brain. In addition, the usual criteria for determining a change in the evoked potential (amplitude reduction by 50% and latency delay by 10%) may not apply when etomidate is administered. Nonetheless, in patients with significant sensory abnormalities, an anesthetic technique based on an etomidate infusion may be considered. Such a technique may allow reasonable EP recording which otherwise may not be possible[8].

3) MOTOR EVOKED POTENTIALS

Motor evoked potential (MEP) monitoring is a relatively new technique that is being increasingly employed during spine surgery that entails a significant risk of injury to the motor tracts. In many instances, the ability to reliably monitor the motor tracts has replaced the intraoeprative wake-up test. In the OR, transcranial electrical rather than magnetic stimulation, applied to the scalp, is used to depolarize cortical pyramidal tracts and to evoke a motor response in the upper and lower extremities. MEP are exquisitely sensitive to anesthetic agents. Volatile agents (in concentrations as low as 0.2-0.3 MAC), barbiturates, propofol and midazolam all significantly suppress MEP[9,10]. It is therefore apparent that the anesthetic technique for MEP monitoring has to be substantially modified. In addition, the administration of muscle relaxants has to be strictly titrated to ensure that muscle contraction in the monitored limb is possible[11].

The recent introduction of a multiple stimulation device has simplified to some extent the anesthetic management. Multiple stimuli, from 2 to 5, with about 75 msec interval between the stimuli, significantly improves the amplitude of the MEP. Moreover, this MEP is less susceptible to anesthetic induced suppression[12]. Accordingly, low doses of volatile agent (~0.3 MAC), propofol- N_2O, propofol-remifentanil[13] and isoflurane- N_2O –opioid[14] techniques may be compatible with adequate MEP monitoring. However, it

should be noted that the administration of isoflurane reduces the percentage of patients in whom reliable MEP recording is possible and it increases the variability in the amplitude of the MEP. Accordingly, it may be prudent to establish robust MEP monitoring before volatile agents are added to the anesthetic regimen.

4) INTRAOPERATIVE ELECTROCORTICOGRAPHY (ECOG)

In patients undergoing craniotomy for resection of seizure producing foci, intraoperative ECoG is often employed. ECoG is used to precisely identify the location of the lesion and the margins of safe brain resection. Seizure foci are identified by characteristic spike waves that are elicited by electrical stimulation of the surrounding brain region. Once the foci are identified, they are removed. ECoG is then used to confirm the removal of the relevant focus – a lack of spike waves will confirm this.

Epilepsy surgery can be performed in an awake or anesthetized patient. Awake craniotomy is usually reserved for cooperative adult patients. Uncooperative patients or pediatric patients are generally anesthetized for the procedure.

During awake craniotomy, patients are usually sedated with an infusion of propofol during the craniotomy. Thereafter, the propofol infusion is discontinued and the patient is allowed to awaken. Upon resumption of consciousness, ECoG mapping is started. Propofol is an ideal agent to use because its pharmacokinetic properties permit rapid emergence from a state of anesthesia. However, it should be remembered that propofol can have a profound effect on the ECoG. Residual propofol in the brain can result in EEG activation in the 18 Hz range[15]. This activation can obscure spike waves from the seizure foci, thereby making precise localization of the foci difficult. The EEG activation can occur even when the patient appears to be fully awake! EEG activation is generally short lived and lasts about 20 min. It is therefore important to discontinue the administration of propofol at least 30 min before the start of ECoG. More recently, the addition of remifentanil to a propofol infusion has permitted a reduction in the dose of propofol; a more rapid emergence (within 10 min) is therefore possible. Anesthetics that suppress seizure foci (benzodiazepine, volatile agents) should, in general, be avoided.

ECoG during general anesthesia is more challenging. Volatile anesthetics, intravenous hypnotics and benzodiazepines can suppress spike waves. Therefore, during ECoG, the use of these agents must be minimized or avoided altogether. An anesthetic technique that is commonly used for this procedure is a combination of N_2O, low dose volatile agent and a narcotic infusion. Shortly before ECoG, the volatile agent is discontinued and the concentration of N_2O is increased to at least 65%. Once the volatile agent is eliminated, ECOG can be performed. During this time, the patient will be lightly anesthetized and there is a significant risk of movement or coughing. It is therefore very important to ensure that the patient is paralyzed. If the spike waves are not detectable, spike activity can be induced by the administration of one of the following:

i) Methohexital, 0.3-0.5 mg/kg[16]. Methohexital results in spike wave activity that emanates primarily from the seizure focus.
ii) Etomidate, 0.1-0.2 mg/kg[17]. The resulting spike wave activity is more generalized that with methohexital.
iii) Alfentanil, 50 µg/kg[18].

5) EPILEPTOGENESIS

Of the currently used anesthetics, two agents have been implicated in the genesis of seizures. Etomidate can activate seizure foci (see above) and can increase spike activity in the brain. However, overt seizure activity with the use of this agent has not been demonstrated. In fact, etomidate has been used to treat refractory status epilepticus. Nonetheless, the possibility of activating the EEG in patients with preexisting epilepsy should be considered before it is used in such patients.

Sevoflurane administration has been shown to cause frank seizure activity in patients. In healthy volunteers, sevoflurane in 1-2 MAC doses has been associated with the development of encephalographic seizure activity. In addition, seizures have been observed in patients who awaken from a sevoflurane anesthetic. Accordingly, caution should be exercised with respect to the administration of sevoflurane to patients with epilepsy.

6) ANESTHETIC NEUROTOXICITY

The adverse impact halothane exposure on the developing brain was reported two decades ago by Levin and colleagues[19]. These investigators demonstrated that long-term exposure to halothane, beginning in utero and continuing for several days in the post-natal period, led to impaired synaptogenesis, reduced dendritic branching, suppressed axonal growth and reduced myelination in rodents. Moreover, halothane exposure during development resulted in impaired neurocognitive function in adulthood. These studies did not achieve notoriety because the manifestation of CNS toxicity required prolonged exposure to halothane, a situation not encountered in clinical practice.

Interest in anesthetic neurotoxicity was renewed by the demonstration that drugs that have antagonist activity at NMDA receptors and agonist activity at GABA-A receptors

produce widespread neurodegeneration in the developing brain[20]. These data led to a re-evaluation of anesthetic neurotoxicity because commonly used anesthetic agents have these effects on NMDA and GABA-A receptors[21]. In a seminal investigation, Jevtovic-Todorovic and colleagues demonstrated that isoflurane (0.75% to 1.5%) resulted in substantial neurodegeneration in a number of structures of the brain, including the hippocampus and neocortex[22]. The addition of midazolam or N_2O to isoflurane increased neuronal death to a greater extent that either of the agents alone. Electrophysiologic function in the hippocampus was significantly reduced in the hippocampus by the anesthetics. In rats that were exposed to anesthetics on post-natal day 7, neurocognitive deficits were apparent at 4-5 weeks of age in comparison to control animals. Collectively, these data indicated that anesthetic agents injure the brain and that this injury results in a long-term impairment of cognitive function. Such neurotoxicity has now been demonstrated for ketamine, midazolam[23], diazepam, pentobarbital[20] and N_2O[22]. While the potential toxicity of propofol has not yet been investigated in detail, it is probable that it too produces neuronal death given its potent activity at GABA-A receptors[24].

Although the data from rodent studies are convincing, its relevance to humans is debatable and it is difficult to extrapolate these findings to the clinical setting. Data from sub-human primates would be expected to have greater relevance to humans. To that end, Slikker et al have evaluated the toxicity of ketamine in frontal cortical neurons cultured from 3 day old monkeys. When exposed to ketamine for 24 hours, these neurons underwent both apoptotic and necrotic cell death. The extent of this injury was reduced by agents that reduced NMDA receptor number[25]. In addition, more recent (yet unpublished data) from this group has shown that ketamine also increases neuronal death in vivo in neonatal monkeys. Of importance is the observation that the nature of neuronal degeneration was similar to that observed in rodents. These data demonstrate clearly that anesthetic agents in common use in patients have the potential to injure the developing brain.

The mechanisms by which anesthetics produce neuronal death are under intense investigation. It is clear that the brain is most susceptible during the period of synaptogenesis[26]. In rodents, this occurs during the first two weeks of post-natal life. Cell death results in impaired or aberrant synaptic connections and it is readily apparent why cell death leads to impaired cognitive function later in life.

Many of the agents that produce neurodegeneration are antagonists of the NMDA receptor. These include ketamine and nitrous oxide. It is clear that glutamate signaling via the NMDA receptor plays a crucial role in synaptic development and neuronal survival. This signaling initiates the activation (phosphorylation) or a number of signal transduction mechanisms, many of which are important in dendritic growth, synaptic stabilization and neuronal survival[26]. During the critical period of synaptogenesis, inhibition of NMDA receptor signaling would be expected to be detrimental to brain development. Indeed, other agents, such as MK801, which are potent NMDA antagonists also produce a pattern of neurodegeneration that is similar to that produced by ketamine.

What is surprising is that GABA-A receptor agonists also produce neuronal death. Anesthetics that are agonists at this receptor include the volatile anesthetics, propofol, barbiturates and benzodiazepines. Each of these is associated with neuronal toxicity. In the adult, GABA-A receptor activation leads to an influx of Cl- into the cell. This results in hyperpolarization of the cell and in many models of hypoxia and ischemia, this can be neuroprotective. However, in the developing brain, especially during synaptogenesis, intracellular concentration of Cl- is high; activation of GABA-A receptor results in Cl- efflux and depolarization of the neuron[27]. Consequently, intracellular calcium concentration reaches levels that can be harmful to the cell. This action of GABA may contribute to neuronal injury.

Based on the above discussion, it has been proposed that an imbalance between excitatory and inhibitory input in the CNS during synaptogenesis produces neuronal injury. According to this model, the imbalance leads to the activation of processes in the neuron that lead to programmed cell death or apoptosis[28]. Apoptosis occurs normally in the developing brain and it is an essential means by which excess cells in the CNS are removed. Apoptosis is the end result of the activation of a cascade of enzymes called caspases. The final caspase in this cascade is caspase-3. This enzyme proteolytically cleaves a variety of cellular substrates that are essential for survival. Neuronal death by apoptosis is an orderly process that is characterized by membrane blebbing and cleavage of the nucleus to produce apoptotic bodies. The apoptotic cell is then removed by phagocytosis. It is important to note that apoptosis does not result in inflammation, which in itself can produce a substantial amount of collateral damage[29].

In order to reveal neurodegeneration induced by anesthetic agents, neonatal pups have to be exposed to anesthetics for a prolonged period of time, usually about 6 hours, during the period of synaptogenesis. In rats, synaptogenesis occurs mainly over a period of about 12 days[30]. Therefore, a 6 h period of anesthesia represents a substantial fraction of the synaptogenesis time. In humans, synaptogenesis occurs during the third trimester and continues until about the age of four[31]. To achieve a similar exposure in humans, neonates would have to be anesthetized for several weeks[32]. This does not occur in the operating room. However, such

prolonged CNS suppression does occur in the intensive care units. Furthermore, during anesthetic exposure, food and nutrition, not to mention pup-maternal bonding, are not provided. Whether this period of "malnutrition" produces neuronal injury is not known. In addition, the potential confounding influences of prolonged anesthesia on respiration (maintenance of normoxia and normocarbia) cannot be properly controlled in neonatal animals. Finally, the doses of drugs used in neonatal rat pups (especially for ketamine) are considerably greater than the doses that are used in patients[32]. Collectively, the available data suggest that there are sufficient differences between species and in the manner in which anesthetics are administered to patients under strict monitoring to render the animal data less relevant to humans. On a more pragmatic level, most of the currently used anesthetic agents have been implicated in neurotoxicity; given the necessity of anesthesia for surgical procedures, anesthetic exposure is unavoidable.

The available data do provide sufficient evidence for a change in current practice. However, pre-clinical experimental data are of serious concern and as such, further intense investigation is necessary. At the present time, there is little to recommend a change in practice. Nonetheless, prolonged anesthesia should be avoided in so far as it is possible. In addition, decision to proceed with anesthesia and surgery in at risk neonates and infants should be made with due consideration of the possibility of anesthetic neurotoxicity.

7) BRAIN PROTECTION

There is a considerable risk of cerebral ischemia during neurosurgical procedures and a substantial investigative effort has focused upon the identification of agents that might reduce ischemic brain injury. Given their propensity to reduce CMR, anesthetics appear to be logical candidates. Volatile agents, barbiturates, propofol and ketamine have all shown neuroprotective efficacy in the laboratory. Unfortunately, this neuroprotection is short lived and is not sustained beyond a period of 2 weeks[33]. Neurons continue to die for a long time after the initial ischemic insult and anesthetics to do mitigate ongoing neuronal loss. In the circumstance of extremely mild ischemic insults, such as those that are likely to occur with brain retraction, anesthetics might produce sustained neuroprotection. However, with such mild insults, it is highly unlikely that differences in the neuroprotective efficacy for individual anesthetics will be manifest. Accordingly, the available data do not support the selection of any given agent for purposes of neuroprotection. Adequate anesthesia, regardless of how it is produced, will increase the tolerance of the brain to ischemia in comparison to the awake state. Barbiturates may be used for purposes of neuroprotection in rare situations (such as prolonged temporary clipping during aneurysm surgery).

Among intravenous hypnotics, the only agent who use might be considered controversial is etomidate. Etomidate can reduce CMR, CMF and ICP. These effects are similar to those produced by barbiturates and propofol. Unlike the latter agents, etomidate does not produce hypotension. Given this favorable pharmacologic profile, the use of etomidate during neurosurgical procedures that entail a risk of cerebral ischemia has been advocated. Unfortunately, it is quite clear from laboratory studies and studies in patients[34] that etomidate does not possess neuroprotective efficacy. In fact, it can *increase* ischemic neuronal injury. The administration of etomidate for the purposes of neuroprotection therefore cannot be advocated. Single doses of etomidate for purposes of anesthetic induction are unlikely to adversely affect neurons and its use in this manner is entirely appropriate.

SUMMARY

In the vast majority of neurosurgical patients, the choice of anesthetic agent is not relevant; the choice of anesthetic agents is unlikely to affect either the surgical field or the patient outcome. The best results are often obtained by the use of a technique with which the anesthesia care provider is familiar. In certain situations, however, the choice of the anesthetic agent can directly impact the surgical field and may have an impact on patient outcome. It is during these situations that a solid command of physiology and the pathophysiology of the CNS and the impact that anesthetic agents have on the brain is essential.

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