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Pharmacologic Strategies for the Treatment of Elevated Intracranial Pressure
Focus on Metabolic Suppression

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ABSTRACT
Elevations in intracranial pressure often occur after traumatic brain injury. A limited array of medications is available for the treatment of intracranial hypertension. Metabolic suppression agents may be used in this situation to suppress electrical activity in the brain, diminish the cerebral metabolic rate of oxygen consumption, and, as a consequence, decrease cerebral blood volume and intracranial pressure. Propofol and pentobarbital have unique characteristics that make each desirable, yet difficult to use in the setting of traumatic brain injury. The subject of this review is to discuss the role of these agents in treating refractory elevated intracranial pressure through metabolic suppression.
Key words: brain injury, intracranial hypertension, intracranial pressure, pentobarbital, propofol

TRAUMATIC BRAIN INJURY (TBI) is a principal factor in many injury-related deaths. Of the annual 1.4 million patients with TBI, approximately 33% die as a result of their insult (Langlois, Rutland-Brown, & Thomas, 2006). The cornerstones of TBI treatment include rapid transportation to a medical facility, maintenance of cerebral oxygenation and perfusion, control of elevated intracranial pressure (ICP), and surgical decompression of hematoma or hemorrhages when necessary (Chesnut, 2007). Many patients with TBI develop intracranial hypertension or elevated ICP, which often requires a number of different interventions to prevent the progression of brain injury and, ultimately, neurologic death.

TBI consists of not only the primary, or initial injury, but also an insidious secondary injury cascade that occurs after the principal insult. Primary injury typically occurs because of direct injury to the brain (ranging from contusions to intracranial bleeding such as a subdural hematoma), which may cause permanent brain damage due to physical tissue destruction. Much of the therapy for primary injury is targeted toward removing intracranial lesions and treating acute

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intracranial hypertension, which occurs because of mass effect from hemorrhage or cerebrospinal fluid (CSF) outflow obstruction. This is primarily accomplished with surgical decompression of hematomas or CSF drainage.

Secondary injury, however, appears to be due to a natural inflammatory cascade that occurs subsequent to primary injury and is typified by brain cell swelling and apoptosis. These effects are mediated by deleterious neurotransmitters such as glutamate, reactive oxygen species, and inflammatory processes governed by complement and cellular immunity. These harmful processes result in excessive calcium influx, cerebral cytotoxic edema, brain metabolic dysfunction, and ultimately cell death due to energy failure. Mannitol or hypertonic saline is often used to treat the resulting elevated ICP by modulating the rheology and osmolarity of the cerebral blood volume. Other medications such as neuromuscular blockers, sedatives such as propofol and barbiturates, are used to suppress metabolism in an effort to abate the "energy stress" present in injured cells. Cerebral perfusion pressure within the goal range of 50–70 mmHg is maintained by controlling elevated ICP and ensuring euvolemia and normal systemic blood pressure (Brain Trauma Foundation, 2007).

The use of neuromuscular blockers, with or without narcotic agents such as morphine, has been advocated by some practitioners to decrease ICP (Robertson, 2001; Rosner, Rosner, & Johnson, 1995). While there is certainly a role for pharmacologic paralysis and analgesia in some patients requiring the aggressive facilitation of mechanical ventilation or in whom cough or excessive agitation increases ICP, there are conflicting data regarding the role for routine neuromuscular blockade for the purposes of ICP control (Hsiang et al., 1994). Failure to appropriately control pain and anxiety prior to or during neuromuscular blockade may result in elevations in ICP. Therefore, therapeutic paralysis should be used only in concert with adequate sedation and pain relief. Neuromuscular blockade may be a useful adjunct to sedative therapy prior to the use of metabolic suppression agents in certain patients but, at this point, the clinical utility of this treatment strategy is undefined.

While metabolic suppression agents are used in contemporary treatment of severe traumatic brain injuries, numerous questions remain unanswered regarding the optimal patient population and circumstances in which metabolic suppression should be used. For example, the balance between adequacy and extent of ICP control and occurrence of severe adverse events can be precarious. Therefore, establishing the optimal duration of pharmacologic coma is desirable. The role of metabolic suppression therapy instead of or in concert with decompressive craniectomy is not only an emerging issue, but also not well-defined. The focus of the following review is to compare and contrast the common agents, propofol and pentobarbital, which may be employed for the purposes of treating refractory, elevated ICP through metabolic suppression.

METABOLIC SUPPRESSION AGENTS

In general terms, metabolic suppression agents induce a pharmacologic coma, which greatly decreases the metabolic requirements of brain cells. Metabolic rate is coupled to cerebral blood flow, so a decrease in metabolism leads to a reduction in cerebral blood volume. The three principal determinants of ICP are brain tissue, CSF, and cerebral blood volume. Therefore, reduced cerebral blood volume typically leads to a decrease in ICP. The propagation of secondary injury through mitochondrial dysfunction and energy depletion may also be attenuated by metabolic suppression. The agents most commonly employed for this treatment strategy include barbiturate anesthetics (thiopental or pentobarbital) and propofol (Table 1). Currently, metabolic suppression is recommended only in salvageable patients with TBI refractory to other conventional therapies such as osmotherapy,

Table 1. Comparison of the characteristics of propofol and pentobarbital

	Propofol	Pentobarbital
Usual dose	25–100 micrograms/kg/min infusion	10 mg/kg over 30 min; then 5 mg/kg every hr for three doses, then maintenance of 1–3 mg/kg/hr infusion
Formulation/diluent	Egg phospholipid emulsion	40% Propylene glycol 10% Ethanol
Monitoring parameters	Blood pressure Triglycerides Creatine kinase, troponin I ICP, EEG	Blood pressure Bowel function Acid–base status Cardiac index ICP, EEG
Primary adverse effects	Hypotension Hypertriglyceridemia Rhabdomyolysis Cardiac failure (PIS)	Hypotension Constipation Myocardial depression Propylene glycol toxicity

Note. EEG = electroencephalogram; ICP = intra-cranial pressure; PIS = propofol-infusion syndrome.

acute hyperventilation, and CSF drainage. Metabolic suppression agents are associated with a number of complications and require thoughtful consideration before initiation and intense monitoring after initiation.

Propofol

Propofol is a short-acting sedative agent that is used in a number of settings where sedation is required. Propofol is not only listed in the joint Society of Critical Care Medicine, American Society of Health-System Pharmacists guidelines for ICU sedation as an alternative to benzodiazepines for sedation to facilitate mechanical ventilation and treat anxiety, but also commonly used at higher doses in the operative theater (Jacobi et al., 2002). The use of high doses of propofol results in the induction of a pharmacologic coma and an isoelectric electroencephalogram (EEG). Limited studies have described the use of propofol for the control of elevated ICP (Table 2). The use of propofol is listed as an option for control of ICP by the most recent Brain Trauma Foundation guidelines for TBI (Brain Trauma Foundation, 2007). Without further study, it is difficult to define the role of propofol in the pharmacologic armamentarium for treating refractory elevated ICP. However, propofol is unique among sedatives and possesses several characteristics that may make it desirable to use in patients requiring frequent neurologic monitoring.

First, propofol is exceptionally lipophilic, which allows for rapid distribution into body tissues, the most important of which is the brain. This property allows for a very rapid onset of action, typically within 2–4 min (McKeage & Perry, 2003). Second, the sedative effects of propofol wane shortly after withdrawing the drug. This is because of extensive tissue penetration and rapid biotransformation in the liver, which is primarily dependent on hepatic blood flow. Typically, if a propofol infusion is held, the patient will arouse to some extent after approximately 10–15 min. This is particularly convenient in patients with TBI when frequent accurate neurological assessment is of paramount importance.

Third, propofol is an effective anticonvulsant. Seizure activity within the first 7 days is evident in approximately 10%–15% of patients with closed TBI who are not receiving

Table 2. Summary of clinical reports utilizing metabolic suppression agents for ICP control

Study design & population	Dosing	Outcomes	Adverse events
Propofol			
Prospective, randomized propofol + morphine vs. morphine, primarily blunt TBI (5 GSW total), $n = 23$ (Kelly et al., 1999)	55 micrograms/kg/min mean propofol infusion rate, titrated to agitation, ICP less than 20 mmHg Not titrated to burst suppression	No significant differences in ICP vs. morphine except Day 3 Less need for neuromuscular blockers, pentobarbital, benzodiazepines in propofol group Trend toward more mannitol, vasopressors 4/23 (17.4%) propofol patients survived	15/23 (65.3%) propofol patients required vasopressors vs. 11/19 (61.5%) morphine patients 1/23 (4.3%) Propofol patients had hypotension requiring withdrawal from study
Pentobarbital			
Refractory to conventional treatments, prospective, multicenter, randomized vs. "continued conventional therapy," primarily blunt TBI (4 GSW total), $n = 37$ (Eisenberg et al., 1988)	10 mg/kg loading dose (slow iv push or iv infusion over 30 min as BP tolerates) 5 mg/kg q1h × 3 Doses 1–3 mg/kg/hr infusion	12/37 (32.4%) Patients had effective ICP control (less than 20 mmHg) 7/26 (26.9%) Cross-over patients had effective ICP control 17/19 responders survived 6/44 nonresponders survived	23/37 (62%) Pentobarbital patients had hypotension requiring vasopressors vs. 18/36 (50%) conventional patients No difference in cardiac complications
Refractory to conventional treatments, retrospective, blunt TBI, $n = 27$ (Rea & Rockswold, 1983)	3–5 mg/kg loading dose 1–3 mg/kg/hr infusion	15/27 (56%) Patients had effective ICP control (less than 20 mmHg) after loading dose 10/15 (67%) Responders within first 24 hr survived 3/12 (25%) nonresponders within first 24 hr survived	No adverse events reported or discussed
Refractory to conventional treatments, retrospective, blunt TBI, $n = 21$ (Lee et al., 1994)	3–5 mg/kg loading dose 1–3 mg/kg/hr infusion 1.5 mg/kg boluses for burst suppression	14/21 (67%) Patients had effective ICP control (less than 20 mmHg) 10/14 Responders survived 1/7 nonresponders survived	No hypotension reported Unknown number of patients did receive vasopressors to maintain adequate CPP
Prospective, randomized vs. "standard therapy," blunt TBI, $n = 27$ (Ward et al., 1985)	5–10 mg/kg loading dose, dosed to burst suppression 1–3 mg/kg/hr infusion, titrated to level of 25–45 mg/L	No difference in ICP between groups 13/27 (48%) Pentobarbital patients survived (at 1 year) 13/26 (50%) Standard therapy patients survived	Significantly more hypotension in pentobarbital patients (14/27, 52%) than standard therapy (2/26, 8%), $p < .001$ Possibly more ARDS, sepsis in pentobarbital patients
Prospective, randomized vs. mannitol, blunt TBI, $n = 28$ (Schwartz et al., 1984)	10 mg/kg loading dose 0.5–3 mg/kg/hr infusion, titrated to maximum level of 45 mg/L	9/28 (32%) pentobarbital patients had effective ICP control vs. 19/31 (61%) mannitol patients 12/28 (43%) pentobarbital patients survived (at 3 months) 18/31 (58%) mannitol patients survived Patients split into hematoma vs. no hematoma (pentobarbital seemed less effective for no hematoma patients)	No hypotension reported Unknown number of patients did experience decrease in CPP, but extent, cause, & treatment assignment are not reported

Note. ARDS = acute respiratory distress syndrome; BP = blood pressure; CPP = cerebral perfusion pressure; GSW = gunshot wound; ICP = intracranial pressure; TBI = traumatic brain injury.

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posttraumatic seizure prophylaxis. Although not specifically studied for this indication, this additional effect is a convenient advantage. Also, in contrast to benzodiazepines, propofol is not associated with a withdrawal syndrome. Finally, propofol appears to have neuroprotectant properties related to its antioxidant activity and suppression of excitatory neurotransmitters released secondary to TBI (Kelly et al., 1999). The precise clinical benefit (if any) of this activity has not yet been elucidated.

Despite all of the desirable characteristics of propofol, its routine use should be undertaken with caution. Several factors may limit or complicate the use of propofol, particularly at high doses or for a prolonged duration. Most acutely, propofol causes dose-related hypotension. In a small study of brain-injured patients comparing propofol to morphine for sedation, propofol caused hypotension in 1 of 23 patients (4.3% vs. 0% for morphine; Kelly et al.,). Others have reported a greater association with hypotension when using propofol for ICU sedation (26%–49%), occurring more often with bolus doses and higher infusion rates (McKeage & Perry, 2003). In the setting of acute TBI, the prevention of hypotension is of paramount importance, necessitating vigilance in blood pressure monitoring when propofol therapy is utilized (Brain Trauma Foundation, 2007).

The lipophilicity of propofol requires a special pharmaceutical preparation to make the drug suitable for intravenous administration. The current formulation of propofol is an egg phospholipid emulsion (1% or 2%), giving the appearance of a milky white liquid. The use of fat to emulsify propofol presents several potential problems. First, hypertriglyceridemia is possible and should be routinely evaluated in patients receiving prolonged infusions. Second, the infusion of intravenous fat may be associated with acute lung injury (Faucher et al., 2003; Lekka, Liokatis, Nathanail, Galani, & Nakos, 2004). However, the evidence with regard to propofol causing acute lung injury is conflicting. While some data suggest that propofol may actually diminish endotoxin-mediated acute lung injury, propofol-induced acute lung injury has also been reported in brain-injured patients (Chu, Liu, Hsu, Lee, & Chen, 2006; El-Ebiary, Torres, Ramirez, Xaubet, & Rodriguez-Roisin, 1995). This carries heightened importance in this population, as impairment of oxygenation is associated with worsened outcome in acute TBI, therefore close monitoring of compliance and gas exchange is necessary (Contant, Valadka, Gopinath, Hannay, & Robertson, 2001).

The lipid vehicle of propofol is also a good medium for bacterial growth. Early reports of contamination of propofol with bacteria such as *Serratia marcescens* and *Staphylococcus aureus* led to the addition of sodium ethylenediaminetetraacetate (EDTA; Bennett et al., 1995). Although the inclusion of this preservative has greatly diminished this concern, the Food and Drug Administration still includes a strict warning regarding the handling of this product and the risk of bacterial contamination. Therefore, strict aseptic technique should be exercised. Propofol infusions (infusion bottle and infusion line) should be changed every 12 hr or at the end of the procedure, whichever is sooner (AstraZeneca, 2005).

Perhaps the most notorious adverse event associated with propofol is propofol-infusion syndrome (PIS). PIS is a constellation of symptoms related to the inhibition of free fatty acid metabolism in muscle cells, leading to cellular energy failure and cell death. The typical symptoms of PIS are bradycardia, fatty infiltration of the liver, lipemia, metabolic acidosis, and rhabdomyolysis (Vasile, Rasulo, Candiani, & Latronico, 2003). In some cases, PIS has progressed to cardiac failure and cardiovascular collapse, particularly in patients already under stress with high cellular energy demand, such as sepsis or brain injury (Cremer et al., 2001). PIS was first reported in a number of patients with pediatric brain injury, but has since been associated with the use of high doses and prolonged duration in adults as well (Bray, 1998; Parke et al., 1992; Vasile et al., 2003). Routine monitoring of creatine kinase, troponin I,

serum myoglobin, triglycerides, and renal function is indicated in those patients receiving propofol at doses more than 80 micrograms/kg/min or for more than 48 hr to detect PIS before clinically evident harm is done.

Pentobarbital

The traditional approach to therapy for elevated ICP typically includes the use of pentobarbital as the long-acting barbiturate of choice. However, particularly in Europe, thiopental is also an option and has similar cerebral metabolic effects. An apt example of the use of thiopental comes from the Lund group in Sweden. Their approach to the treatment of patients with TBI differs from the traditional approach, which focused primarily on reduction in ICP (Robertson, 2001). Thiopental tends to be a more prevalent component of the Lund group's initial therapy for elevated ICP with the intention of reducing cerebral blood volume and overall systemic hydrostatic pressure, in keeping with their overall philosophy of minimizing the development of cerebral edema. Although some aspects of these two treatment philosophies may differ widely, no one method of treating TBI has been shown to be superior at this point in time. The focus of this pentobarbital discussion will be its use in the context of traditional ICP management.

Pentobarbital is a long-acting barbiturate capable of producing a pharmacologic coma. Like propofol, pentobarbital is quite lipophilic, allowing for rapid distribution into the central nervous system and a nearly immediate onset of action. In order to solubilize the drug for intravenous administration, the current pentobarbital formulation includes 40% propylene glycol and 10% ethanol and is buffered to a pH of 9.5. This may lead to some phlebitis if given through peripheral veins. However, because of the cardiovascular adverse events and the nature of patients with TBI requiring pentobarbital therapy, central venous access should be in place prior to initiating this medication.

Notably in contrast to propofol, pentobarbital has an extended half-life (approximately 19 hr), thus rapid emergence from coma after cessation of the infusion should not be expected (Wermeling, Blouin, Porter, Rapp, & Tibbs, 1987). For this reason, pentobarbital should not be used in patients requiring arousal or frequent neurological examinations. In addition, pentobarbital is cleared hepatically and is influenced directly by the metabolic capacity of the liver. Patients with TBI often have elevated metabolism as a result of their injury, leading to enhanced pentobarbital clearance when compared to the normal population (Wermeling et al., 1987). Pentobarbital also induces its own metabolism as well as that of other hepatically metabolized medications, leading to a number of clinically relevant drug–drug interactions, such as increased clearance of valproic acid, phenytoin, and corticosteroids.

Pentobarbital is a relatively reliable agent with regard to lowering ICP in adults. The classification of treatment success varies somewhat in the available studies that evaluate the efficacy of pentobarbital, but it appears that 32.4%–83% of patients will have some measurable ICP control with pentobarbital therapy (Eisenberg, Frankowski, Contant, Marshall, & Walker, 1988; Lee, Deppe, Sipperly, Barrette, & Thompson, 1994). As might be expected, patients with adequate ICP control due to pentobarbital typically have a better survival rate than those who continue to have uncontrolled ICP despite metabolic suppression therapy (Lee et al., 1994; Rea & Rockswold, 1983). In general, the use of long-acting barbiturates like pentobarbital is not recommended as primary therapy for elevated ICP. Rather, this therapy should be reserved for salvageable patients refractory to other methods of ICP control such as cerebrospinal fluid (CSF) drainage, osmotherapy, acute hyperventilation, and pharmacologic paralysis and sedation (Brain Trauma Foundation, 2007; Robertson, 2001).

The use of pentobarbital is fraught with complications. Hypotension and other cardiovascular manifestations are common with

pentobarbital use (Eisenberg et al., 1988). After the initial bolus, the mean arterial pressure may decrease, thereby decreasing cerebral perfusion pressure. This is due in part to the abolition of central sympathetic discharge and a relative decrease in circulating stress factors as a result of the coma. In addition, the propylene glycol diluent may cause hypotension. When administering boluses of pentobarbital, slow infusion rates and close blood pressure monitoring are essential. Pentobarbital is also a myocardial depressant that decreases cardiac output (Rubanyi & Kovach, 1980). This effect is most evident after extended therapy (typically greater than 72 hr). Many patients will require hemodynamic support with fluid boluses and, in many instances, a vasopressor or inotropic agent. For this reason, invasive arterial blood pressure monitors and/or a pulmonary artery catheter are often recommended when inducing a barbiturate coma. The diminished cardiac function is reversible and cardiac output typically returns to normal after cessation of the infusion and following the subsequent prolonged elimination time period.

Pentobarbital is also associated with the development of infection, and there are various reasons for this phenomenon. First, the likelihood of pneumonia is greater in patients in a pentobarbital coma. Pentobarbital suppresses the normal cough reflex, inhibiting effective clearance of sputum. In addition, due in part to the severity of neurologic illness, and the profound sedation imparted by the pharmacologic coma, patients require mechanical ventilation for a prolonged period, which increases the risk of ventilator-associated pneumonia. Second, the risk of cardiovascular adverse events necessitating invasive blood pressure and/or hemodynamic monitoring leads to a prolonged period with indwelling intravenous catheters. Finally, pentobarbital itself possesses immunosuppressive properties. Inhibitory effects on T-cell lymphocytes and inflammatory cytokines are associated with prolonged pentobarbital use, even beyond the immunosuppression conferred by acute brain injury (Dziedzic, Slowik, & Szczudlik, 2004; Loop et al., 2003). Patients receiving pentobarbital are likely to acquire an infection, and clinicians should maintain a high index of suspicion in evaluating potential symptoms of infection.

Pentobarbital may be a factor in enteral feeding intolerance, particularly after prolonged infusions; thus, aggressive bowel regimens are typically necessary to facilitate enteral nutrition. Fortunately, metabolic requirements, which are typically elevated in patients with TBI, are lessened by nearly 40% because of pentobarbital. Therefore, less enteral nutrition per day is required to meet the estimated caloric needs of a patient with TBI (Dempsey, Guenter, & Mullen, 1985). Conflicting evidence exists regarding the feasibility of providing enteral nutrition during pentobarbital therapy, but given the general benefits of feeding the gut over parenteral nutrition, a trial of postpyloric enteral nutrition is indicated (Bochicchio et al., 2006; Magnuson, Hatton, Williams, & Loan, 1999; Marik & Pinsky, 2003).

MONITORING AND DOSING OF METABOLIC SUPPRESSION AGENTS

As discussed above, propofol and pentobarbital each have characteristic adverse effects that should be anticipated and systematically monitored. In any patient with TBI with elevated ICP, global indices of perfusion and oxygenation including mean arterial pressure, cerebral perfusion pressure, and arterial oxygen saturation should be evaluated regularly. However, when using either of these agents for elevated ICP, additional tools may be useful in guiding therapy such as pharmacokinetic monitoring, continuous EEG monitoring, or possibly bispectral index (BIS) monitoring.

Pharmacokinetic monitoring of pentobarbital is possible in most institutions. Serum concentrations of pentobarbital may be obtained and typically correlate well with the dose administered. In the average patient with TBI, the serum concentration will change as 1 microgram/ml for each 1 mg/kg administered (Wermeling et al.). However, although

the putative therapeutic range is usually stated as 20–40 mg/L, serum concentrations do not correlate well with ICP response. Cormio, Gopinath, Valadka, and Robertson (1999) classified patients as having good, partial, or no ICP response after receiving pentobarbital. Although the changes in ICP (and cerebral metabolic rate of oxygen) were significantly different among the three groups, the postloading dose and maximum pentobarbital concentrations were not different, illustrating the lack of correlation between serum concentration and ICP response (Cormio et al., 1999). Therefore, serum pentobarbital concentrations should not be routinely sampled for the purposes of infusion titration. Serum samples may be helpful in patients exhibiting toxicity at normal doses or 24–48 hr after cessation of the infusion, in order to exclude the possibility of a continued pharmacologically induced coma in a potentially brain-dead patient.

Although ICP is generally the recommended endpoint for metabolic suppression therapy, burst suppression as evidenced by continuous EEG is often used as a surrogate endpoint for the adequacy of the therapy. Pentobarbital and, at certain doses, propofol are able to produce an isoelectric EEG. Complete burst suppression usually leads to near maximal decreases in cerebral metabolism and cerebral blood flow (Brain Trauma Foundation, 2007). Clinicians may also opt to titrate the infusion to near burst suppression (i.e., 3–5 bursts per minute) to avoid excessive drug administration, depending on the patient's ICP response.

The BIS monitor has become a favored tool in some practices for the monitoring of ICU sedation. As it incorporates EEG technology and produces an easy-to-evaluate number correlating to the relative degree of sedation, it is reasonable to expect the BIS monitor to have some utility in monitoring metabolic suppression therapy in lieu of a continuous EEG. Although published experience is still somewhat limited, there does appear to be a correlation of BIS score to burst suppression ($r = .90$). In one study, a BIS score of 10–20 correlated to approximately 3–5 bursts per minute on continuous EEG (Riker, Fraser, & Wilkins, 2003). The BIS is useful in the immediate period of initiation of pentobarbital or high-dose propofol, because it can be set up quickly (as opposed to a continuous EEG) and the single wave-form may serve as a rough estimate for when isoelectric activity is attained. The utility of routine BIS monitoring to guide metabolic suppression therapy will not likely replace ICP monitoring and still requires more validation.

The dosing of propofol and pentobarbital is often a source of confusion for practitioners because of the indication for therapy. Propofol may be familiar to clinicians, but most often in the context of sedation of mechanically ventilated patients or short-term anesthesia in the operating room. Pentobarbital is a rarely used therapy with a wide range of published dosing protocols and pharmacokinetic properties that are unlike many of the contemporary commonly used sedatives. Inappropriate dosing (and monitoring) of these agents may lead to either a delay in ICP control in an already dire situation or excessive drug exposure that may lead to toxicity or a prolonged comatose state. For these reasons, knowledge of the recommended and optimal dosing strategies is of paramount importance.

In general, the most rapid way to achieve the maximal effect of a drug is to administer a bolus dose. Propofol may be administered as a bolus (usually 1 mg/kg), but these bolus doses may lead to acute hypotension. Because of the rapid elimination of propofol in the serum, however, the maximal effects of a propofol infusion will be evident within 15–20 min of initiation. Therefore, the omission of a bolus dose for propofol may be preferable, particularly in patients in whom a drop in cerebral perfusion pressure is of concern. The doses of propofol required to achieve burst suppression are much higher than typically used in the ICU setting. Doses ranging from 50 to 100 micrograms/kg/min are often needed to attain an isoelectric EEG (Johnston et al., 2003). Although conflicting data exist regarding the effects of propofol

on cerebral blood flow-metabolism coupling, propofol does appear to be safe in patients with TBI (Johnston et al., 2003; Kelly et al., 1999). However, it is unclear whether burst suppression is necessary for optimal effects and randomized studies comparing propofol to other metabolic suppression therapies such as barbiturates are not available.

Pentobarbital dosing is quite different from propofol because of the dissimilar pharmacokinetics of the two drugs. Pentobarbital requires a large loading dose to rapidly achieve a concentration that is likely to be therapeutic. After a sufficient loading dose has been administered, a continuous infusion may be initiated. Any changes in the pentobarbital infusion rate are not likely to be evidenced by increased ICP control for many hours because of the long half-life of the drug. For this reason, for breakthrough ICP elevations, small bolus doses should be given to rapidly achieve a higher serum concentration. Titrating the infusion rate without bolus dosing should be avoided, as it will lead to delayed ICP control, and ultimately, the administration of high doses of the continuous infusion, which are likely to lead to toxicity. Representative pentobarbital dosing protocols are detailed in Table 2.

SUMMARY

Metabolic suppression therapy is a useful method of controlling refractory, elevated ICP. The Brain Trauma Foundation guidelines suggest that the use of barbiturates to induce a pharmacologic coma should be reserved for treating those with elevated ICP refractory to other methods of treatment such as osmotherapy and acute hyperventilation (Brain Trauma Foundation, 2007). Both propofol and pentobarbital may be used to induce a pharmacologic coma, although the majority of the published experience and recommendations suggest barbiturates as the first-line agent. Each agent has specific peculiarities with regard to formulation, adverse effects, and optimal dosing strategies. Either of these agents should be used on the basis of the prognosis of the TBI patient, the likelihood of toxicity, and the goals of therapy. Judicious patient selection and close monitoring are of paramount importance to maximize the benefit of metabolic suppression therapy.

REFERENCES

AstraZeneca. (2005). Diprivan intensive care sedation technical monograph–International edition. Retrieved July 28, 2007, from http://www.astrazeneca-US.com/pi/diprivan.pdf

Bennett, S. N., McNeil, M. M., Bland, L. A., Arduino, M. J., Villarino, M. E., Perrotta, D. M., et al. (1995). Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *New England Journal of Medicine, 333*, 147–154.

Bochicchio, G. V., Bochicchio, K., Nehman, S., Casey, C., Andrews, P., & Scalea, T. M. (2006). Tolerance and efficacy of enteral nutrition in traumatic brain-injured patients induced into barbiturate coma. *Journal of Parenteral and Enteral Nutrition, 30*(6), 503–506.

Brain Trauma Foundation. (2007). Guidelines for the management of severe traumatic brain injury. *Journal of Neurotrauma, 24*, S1–S95.

Bray, R. J. (1998). Propofol infusion syndrome in children. *Paediatric Anaesthesia, 8*, 491–499.

Chesnut, R. M. (2007). Care of central nervous system injuries. *Surgical Clinics of North America, 87*, 119–156.

Chu, C-H., Liu, D. D., Hsu, Y-H., Lee, K-C., & Chen, H. I. (2007). Propofol exerts protective effects on the acute lung injury induced by endotoxin in rats. *Pulmonary Pharmacology and Therapeutics, 20*(5), 503–512.

Contant, C. F., Valadka, A. B., Gopinath, S. P., Hannay, H. J., & Robertson, C. S. (2001). Adult respiratory distress syndrome: A complication of induced hypertension after severe head injury. *Journal of Neurosurgery, 95*, 560–568.

Cormio, M., Gopinath, S. P., Valadka, A. B., & Robertson, C. S. (1999). Cerebral hemodynamic effects of pentobarbital coma in head-injured patients. *Journal of Neurotrauma, 16*(10), 927–936.

Cremer, O. L., Moons, K. G. M., Bouman, E. A. C., Kruijswijk, J. E., de Smet, A. M., & Kalkman, C. J. (2001). Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet, 357*, 117–118.

Dempsey, D. T., Guenter, P. A., Mullen, J. L., Fairman, R., Crosby, L. O., Speilman, G., et al. (1985). Energy expenditure in acute trauma to the head with and without barbiturate therapy. *Surgery, Gynecology and Obstetrics, 160*, 128–134.

Dziedzic, T., Slowik, A., & Szczudlik, A. (2004). Nosocomial infections and immunity: Lesson from brain-injured patients. *Critical Care, 8*(4), 266–270.

Eisenberg, H. M., Frankowski, R. F., Contant, C. F.,

Marshall, L. F., & Walker, M. D. (1988). High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *Journal of Neurosurgery, 69*, 15–23.

El-Ebiary, M., Torres, A., Ramirez, J., Xaubet, A., & Rodriguez-Roisin, R. (1995). Lipid deposition during the long-term infusion of propofol. *Critical Care Medicine, 23*(11), 1928–1930.

Faucher, M., Bregeon, F., Gainnier, M., Thirion, X., Auffray, J. P., & Papazian, L. (2003). Cardiopulmonary effects of lipid emulsions in patients with ARDS. *Chest, 124*, 285–291.

Hsiang, J. K., Chesnut, R. M., Crisp, C. B., Klauber, M. R., Blunt, B. A., & Marshall, L. F. (1994). Early, routine paralysis for intracranial pressure control in severe head injury: Is it necessary? *Critical Care Medicine, 22*(9), 1471–1476.

Jacobi, J., Fraser, G. L., Coursin, D. B., Riker, R. R., Fontaine, D., Wittbrodt, E. T., et al. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine, 30*(1), 119–141.

Johnston, A. J., Steiner, L. A., Chatfield, D. A., Coleman, M. R., Coles, J. P., Al-Rawi, P. G., et al. (2003). Effects of propofol on cerebral oxygenation and metabolism after head injury. *British Journal of Anaesthesia, 91*(6), 781–786.

Kelly, D. F., Goodale, D. B., Williams, J., Herr, D. L., Chappell, E. T., Rosner, M. J., et al. (1999). Propofol in the treatment of moderate and severe head injury: A randomized, prospective double-blinded pilot trial. *Journal of Neurosurgery, 90*, 1042–1052.

Langlois, J. A., Rutland-Brown, W., & Thomas, K. E. (2006). *Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Lee, M. W., Deppe, S. A., Sipperly, M. E., Barrette, R. R., & Thompson, D. R. (1994). The efficacy of barbiturate coma in the management of uncontrolled intracranial hypertension following neurosurgical trauma. *Journal of Neurotrauma, 11*(3), 325–331.

Lekka, M. E., Liokatis, S., Nathanail, C., Galani, V., & Nakos, G. (2004). The impact of intravenous fat emulsion administration in acute lung injury. *American Journal of Respiratory and Critical Care Medicine, 169*, 638–644.

Loop, T., Humar, M., Pischke, S., Hoetzel, A., Schmidt, R., Pahl, H. L., et al. (2003). Thiopental inhibits tumor necrosis factor alpha-induced activation of nuclear factor kappaB through suppression of kappaB kinase activity. *Anesthesiology, 99*(2), 360–367.

Magnuson, B., Hatton, J., Williams, S., & Loan, T. (1999). Tolerance and efficacy of enteral nutrition for neurosurgical patients in pentobarbital coma. *Nutrition in Clinical Practice, 14*, 131–134.

Marik, P. E., & Pinsky, M. (2003). Death by parenteral nutrition. *Intensive Care Medicine, 29*, 867–869.

McKeage, K., & Perry, C. M. (2003). Propofol: A review of its use in intensive care sedation of adults. *CNS Drugs, 17*(4), 235–272.

Parke, T. J., Stevens, J. E., Rice, A. S., Greenaway, C. L., Bray, R. J., Smith, P. J., et al. (1992). Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. *British Medical Journal, 305*, 613–616.

Rea, G. L., & Rockswold, G. L. (1983). Barbiturate therapy in uncontrolled intracranial hypertension. *Neurosurgery, 12*(4), 401–404.

Riker, R. R., Fraser, G. L., & Wilkins, M. L. (2003). Comparing the bispectral index and suppression ratio with burst suppression of the electroencephalogram during pentobarbital infusions in adult intensive care patients. *Pharmacotherapy, 23*(9), 1087–1093.

Robertson, C. S. (2001). Management of cerebral perfusion pressure after traumatic brain injury. *Anesthesiology, 95*, 1513–1517.

Rosner, M. J., Rosner, S. D., & Johnson, A. H. (1995). Cerebral perfusion pressure: Management protocol and clinical results. *Journal of Neurosurgery, 83*, 949–962.

Rubanyi, G., & Kovach, A. G. (1980). Effect of pentobarbital anesthesia on contractile performance and oxygen-consumption of perfused rat heart. *Circulatory Shock, 7*(2), 121–127.

Schwartz, M. L., Tator, C. H., Rowed, D. W., Reid, S. R., Meguro, K., & Andrews, D. F. (1984). The University of Toronto head injury treatment study: A prospective, randomized comparison of pentobarbital and mannitol. *Canadian Journal of Neurological Sciences, 11*, 434–440.

Vasile, B., Rasulo, F., Candiani, A., & Latronico, N. (2003). The pathophysiology of propofol infusion syndrome: A simple name for a complex syndrome. *Intensive Care Medicine, 29*, 1417–1425.

Ward, J. D., Becker, D. P., Miller, J. D., Choi, S. C., Marmarou, A., Wood, C., et al. (1985). Failure of prophylactic barbiturate coma in the treatment of severe head injury. *Journal of Neurosurgery, 62*, 383–388.

Wermeling, D. P., Blouin, R. A., Porter, W. H., Rapp, R. P., & Tibbs, P. A. (1987). Pentobarbital pharmacokinetics in patients with severe head injury. *Drug Intelligence and Clinical Pharmacy, 21*(5), 459–463.