

Chapter 11. Barbiturates

I. RECOMMENDATIONS

Strength of Recommendation: Weak.
Quality of Evidence: Low from poor-quality class III studies.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

There are insufficient data to support a level II recommendation for this topic.

C. Level III

High-dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management.

When high-dose barbiturate therapy is used to treat refractory intracranial hypertension, continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate cerebral perfusion pressure are required.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Children with severe traumatic brain injury (TBI) may develop intracranial hypertension resistant to medical and surgical management. Reported rates of refractory intracranial hypertension vary (21% to 42%) (1–6). A recent study of 132 children from South America found that 43% experienced refractory intracranial hypertension that was treated with either high-dose barbiturates or decompressive craniectomy (7). Children have more diffuse swelling and higher rates of generalized hyperemia after severe TBI and compared with adults (8, 9) and young children have greater risk of intractable intracranial hypertension compared with older children (7).

Barbiturates lower intracranial pressure (ICP) when first-tier medical and surgical management have not resulted in adequate control. However, cardiorespiratory side effects are very common and potentially toxic, including decreased cardiac output, hypotension, and increased intrapulmonary shunt resulting in lower cerebral perfusion pressure and hypoxia. Thus, high-dose barbiturate therapy has been reserved for extreme cases of intracranial hypertension resistant to first-tier medical and surgical care.

The use of high-dose barbiturates is based on the logic that uncontrolled intracranial hypertension leads to ongoing secondary brain injury and a high risk of death or poor cognitive outcomes. Thus, control of ICP may improve patient survival and outcome. A recent randomized controlled study of 225 traumatic brain-injured children that used a tiered therapy protocol for management of ICP and cerebral perfusion pressure treated 16% of patients with barbiturates as a late therapy (10). So, although high-dose barbiturates are reserved for a high-risk group, use in North American pediatric severe TBI care is common.

High-dose barbiturates lower ICP through two distinct mechanisms: suppression of metabolism and alteration of vascular tone (11–13). Barbiturate therapy improves coupling of regional blood flow to metabolic demands resulting in higher brain oxygenation (14) with lower cerebral blood flow and decreased ICP from decreased cerebral blood volume. Other brain protective mechanisms include inhibition of oxygen radical mediated lipid peroxidation as well as inhibition of excitotoxicity (15).

Few studies have evaluated high-barbiturate pharmacokinetics and pharmacodynamics in head-injured children (16–19). Clearance appears to vary widely and may be increased with duration of barbiturate administration (17). Barbiturate levels are poorly correlated with electrical activity (18, 19). Monitoring electrographic patterns to achieve burst suppression is thought to be more reflective of therapeutic effect than drug levels.

Near maximum reduction in cerebral metabolism and cerebral blood flow occurs when burst suppression is induced.

High-dose barbiturates suppress metabolism and, although both use of pentobarbital and thiopental have been reported, there is insufficient information about comparative efficacy to recommend one over another, except in relation to their particular pharmacologic properties.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 47 potentially relevant studies, none were added to the existing table and used as evidence for this question.

V. SCIENTIFIC FOUNDATION

Two class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (1, 20).

A study by Kasoff et al (1) reported a case series of 25 children with severe TBI. ICP was monitored in all patients and surgical lesions treated. Standard care for elevated ICP (in 1988) included targeted hyperventilation to partial pressure of arterial carbon dioxide 25–30 mm Hg, administration of dexamethasone, and mannitol for osmolar therapy. If ICP remained >20 mm Hg, patients received pentobarbital as an initial bolus of 4–7 mg/kg followed by a continuous infusion of 1–4 mg/kg/hr to a goal of clinical coma. All patients treated with high-dose barbiturates (n = 11) were monitored with a pulmonary artery catheter. Goals were to maintain ICP <20 mm Hg, cerebral perfusion pressure >40 mm Hg, and hemodynamic stability. Ninety-one percent (ten of 11) required dopamine to maintain blood pressure goals compared with 11% of children who did not receive barbiturate therapy. Eighty-two percent (nine of 11) developed hypotension (mean arterial pressure <80 mm Hg).

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines Kasoff et al, 1988 (1)	Design: case series N = 11 Age: 3 months to 17 yrs Protocol: patients were treated with high-dose pentobarbital for intracranial hypertension despite first-line therapy Outcome: hemodynamic monitoring, use of inotropic agents, and hospital mortality were assessed	Class III Poor quality: observational study with no control for confounding	4 of 11 (36%) died Hypotension (mean arterial pressure <80 mm Hg) occurred in 9/11 (82%) Systemic vascular resistance was depressed, left ventricular stroke work decreased, cardiac index depressed, pulmonary shunt fraction increased with pentobarbital therapy
Pittman et al, 1989 (20)	Design: case series N = 27 Age: 2 months to 15 yrs Protocol: patients were treated with high-dose pentobarbital for intracranial hypertension despite first-line therapy Outcome: cerebral perfusion pressure, intracranial pressure, and 1-yr outcome were reported	Class III Poor quality: observational study with no control for confounding	14 of 27 (52%) achieved intracranial pressure <20 mm Hg Of 13 with persistently elevated intracranial pressure, 6 died (22%), 2 were vegetative, 2 had moderate recovery, and 3 good recovery

The authors noted that children treated with high-dose barbiturates had diminished cardiac output, lower systemic vascular resistance, decreased left ventricular stroke volume, and increased intrapulmonary shunt. Thirty-seven percent of children treated with high-dose barbiturates died. The effects of barbiturate therapy on ICP and cerebral perfusion pressure were not reported.

A study by Pittman et al (20) reported a case series of 27 children with severe TBI treated with addition of pentobarbital if ICP remained >30 mm Hg after treatment with hyperventilation to a goal arterial carbon dioxide 25–30 mm Hg, serum osmolality >300 mOsm, cerebrospinal fluid drainage, and evacuation of surgical mass lesions. A pentobarbital dose of 5 mg/kg followed by an infusion of 1–2 mg/kg/hr with a goal barbiturate level of 30–40 mg% was used. Fourteen children (52%) responded to pentobarbital and ICP was controlled (<20 mm Hg). Mortality in this subgroup was not reported. Thirteen children had persistent intracranial hypertension despite addition of high-dose barbiturates. Six died within 48 hrs of starting barbiturates. Seven children had prolonged (>2 days) duration of elevated ICP with pressure >35 mm Hg for “extended” periods of time. Glasgow Outcome Scale score was assessed at 6 months and 1 yr after injury in the seven children who survived. Three improved to make a good recovery, two were left

with severe disability, and two were vegetative. Among children with elevated ICP despite the addition of high-dose barbiturates, poor outcome (severe disability–death) was reported in ten of 13 (77%). Glasgow Outcome Scale score was not reported for the 14 children with controlled ICP. In this series of children with intractable intracranial hypertension, addition of high-dose barbiturates controlled ICP in just over half the patients; however, the authors did not report rates of cardiovascular complications, mortality, or survival with neurologic morbidity, preventing conclusions regarding barbiturate-related control of ICP and its effect on outcome. Among children with uncontrolled ICP despite addition of high-dose barbiturates, good survival was possible (33%); however, this estimate is based on a small number (n = 13).

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

There are no published studies of prophylactic barbiturate use in children with severe TBI. The studies in adults are summarized in the *Guidelines for the Management of [Adult] Severe Traumatic Brain Injury* (21). There are two randomized clinical trials that examined early prophylactic administration of barbitu-

rates. Neither reported clinical benefit (22, 23). A study by Schwartz et al (22) did not define the lower age limit in their study and although the study by Ward et al (23) included adolescents aged >12 yrs, they did not separately report the effects of early barbiturate therapy among children. The study by Ward et al (23) reported that 54% of barbiturate-treated patients developed hypotension compared with 7% of control patients. Hypotension is a well-described risk factor for mortality and neurologic morbidity in head-injured pediatric patients (24).

A study by Eisenberg et al (25) reported a multicentered randomized clinical trial of high-dose barbiturates in severely head-injured patients with intractable intracranial hypertension. Patient age ranged from 15 to 50 yrs but results for the pediatric patients were not separately reported. ICP was the primary outcome and patients in the control group could be crossed over to barbiturate therapy at prespecified ICP failure points in the study. Among 68 study patients, 32 were randomized to high-dose barbiturate therapy and 32 of the 36 control patients ultimately crossed over to barbiturate therapy. Therapy before initiating barbiturates included hyperventilation, neuromuscular blockade, sedation, osmolar therapy with mannitol, steroids, and cerebrospinal fluid drainage when possible. The odds of ICP control were twofold greater in the barbiturate group

and survival 1 month after injury was 92% for responders compared with 17% for nonresponders. At 6 months, 36% of responders were vegetative compared with 90% of nonresponders. The crossover design of this study precludes firm conclusions about the efficacy of high-dose barbiturates to control intractable ICP and improve outcome.

A number of barbiturate dosing regimens have been reported. The study by Eisenberg et al (25) used the following regimen for pentobarbital: a loading dose 10 mg/kg over 30 mins, then 5 mg/kg every hour for three doses, and a maintenance dose of 1 mg/kg/hr.

B. Information Not Included as Evidence

The Cochrane Review (26) has a pooled analysis from three trials of barbiturates and calculated the pooled risk estimated for barbiturate therapy on mortality was 1.09 (95% confidence interval, 0.81–1.47). They found that one in four barbiturate-treated patients developed hypotension and concluded that there is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome.

A study by Nordby et al (27) used thiopental in a study that included children and adults with loading doses of 20–30 mg/kg and a maintenance of 3–5 mg/kg/hr. Doses of thiopental were reduced if blood pressure fell or ICP was <25 mm Hg.

The duration and optimal method to discontinue high-dose barbiturates have not been studied. Clinicians typically wait for at least a 24-hr period of ICP control without sustained elevations with stimulation before beginning to taper the barbiturate infusion (28).

Refractory Intracranial Hypertension

Use of high-dose barbiturates to treat elevated ICP in children with severe TBI has been reported since the 1970s. Marshall et al (29) were the first to report that both control of ICP and outcomes were improved with use of barbiturates; however, patient age was not specified in the report, which was a case series of 25 patients with ICP >40 mm Hg treated with high-dose pentobarbital. When ICP was controlled, mortality was significantly reduced compared with patients with persistently elevated ICP despite

addition of barbiturate therapy (21% vs. 83%).

VII. SUMMARY

Studies regarding high-dose barbiturate administration to treat severe TBI in pediatric patients are limited to two case series (class III evidence), which limits firm conclusions. The evidence suggests that barbiturates effectively lower ICP among a subset of children with intractable intracranial hypertension; however, a beneficial effect on survival or improved neurologic outcome has not been established. Administration of high-dose barbiturates is commonly associated with hypotension and the need for blood pressure support in both children and adults. Studies have not evaluated whether the risk of cardiovascular side effects differ by patient age. Administration of high-dose barbiturates to infants and children requires appropriate monitoring to avoid and rapidly treat hemodynamic instability and should be supervised by experienced critical care providers.

There is no evidence to support use of prophylactic barbiturates to prevent intracranial hypertension or for neuroprotective effects in children.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- High-dose barbiturates are used to treat intractable intracranial hypertension in children. Studies are needed to better quantify their effect on ICP, long-term outcome, the risk of concurrent hemodynamic instability, and their association with morbidity and mortality. In addition, direct comparison to other therapies for refractory intracranial hypertension is needed.
- Age-dependent toxicity of high-dose barbiturates has not been evaluated.
- The effectiveness of high-dose barbiturate therapy for children with different anatomical lesions, including diffuse swelling, has not been evaluated for either control of ICP or outcome.
- High-dose barbiturate therapy to control intractable intracranial hypertension among infants with abusive head injury has not been described. These infants have poor cognitive outcomes (30).

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head trauma patients with elevated intracranial pressure. *Pediatr Neurosci* 1988; 14: 241–249

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