

Chapter 13. The use of barbiturates in the control of intracranial hypertension in severe pediatric traumatic brain injury

I. RECOMMENDATIONS

A. Standards. There are insufficient data to support a treatment standard for this topic.

B. Guidelines. There are insufficient data to support a treatment guideline for this topic.

C. Options. High-dose barbiturate therapy may be considered in hemodynamically stable patients with salvageable severe head injury and refractory intracranial hypertension.

If high-dose barbiturate therapy is used to treat refractory intracranial hypertension, then appropriate hemodynamic monitoring and cardiovascular support are essential.

D. Indications from Adult Guidelines. The adult guidelines (1) recommend consideration of high-dose barbiturate therapy in “hemodynamically stable patients with salvageable severe TBI and intracranial hypertension refractory to maximal medical and surgical intracranial pressure-lowering therapy” as a guideline.

II. OVERVIEW

It is estimated that 21–42% of children with severe traumatic brain injury (TBI) will develop intractable elevated intracranial pressure (ICP) despite medical and surgical management (3–8). The reported mortality rates are 29–100% when the ICP is >40 mm Hg despite therapy to lower ICP.

The ICP-reducing and direct neuroprotective properties of barbiturates have prompted the investigation of two approaches for their use in the management of patients with severe traumatic brain injury: a) prophylactic administration early after injury, and b) use in the treatment of refractory ICP.

III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search

strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 19 potentially relevant studies, two were used as evidence for this question (Table 1).

IV. SCIENTIFIC FOUNDATION

High-dose barbiturates are known to reduce ICP; however, side effects have limited their use to cases refractory to first-line therapies (4, 9, 10). Barbiturates appear to exert their ICP-lowering effects through two distinct mechanisms: suppression of metabolism and alterations in vascular tone (11–13). Barbiturates can lower resting cerebral metabolic rate for oxygen by about 50% (11). When cerebral blood flow and cerebral blood volume are coupled to regional metabolic rate, they are also decreased. This mechanism mediates the observed beneficial effects of barbiturates on ICP and cerebral perfusion pressure. However, Cruz (14) reported that some patients treated for intractable ICP with barbiturate coma developed jugular venous oxygen saturation levels <45%, which was associated with a significantly worse outcome compared with patients with higher jugular venous oxygen saturations. This suggested that in some patients, barbiturate coma induced oligemic hypoxia. Cruz included teenagers and adults; however, the results of the teenagers were not separately reported. Barbiturates confer additional direct neuroprotective effects independent of their ICP-lowering properties, such as inhibition of free radical-mediated lipid peroxidation or membrane stabilization (11).

Few studies have evaluated barbiturate pharmacokinetics and pharmacodynamics in children with head injury (15–18). Clearance appears to vary widely and may be increased with duration of therapy (18). Barbiturate serum levels are poorly correlated with electrical activity

(16, 17). Monitoring of electroencephalographic patterns for burst suppression is thought to be more reflective of therapeutic effect than measuring serum drug levels (11, 13). Near-maximum reduction in cerebral metabolism and cerebral blood flow occurs when burst suppression is induced (9, 13).

Barbiturates suppress metabolism; however, there is insufficient information about comparative efficacy to recommend one barbiturate over another, except in relation to their particular pharmacologic properties. The use of both pentobarbital and thiopental has been reported.

Prophylactic Use of Barbiturates

There are no published studies of prophylactic barbiturate use in children with severe TBI. The “Guidelines for the Management of [Adult] Severe Traumatic Brain Injury” (1) reported on two randomized clinical trials that examined early prophylactic administration of barbiturates. Neither study demonstrated clinical benefit (19, 20). Schwartz et al. (20) did not define the lower age limits in their study, but the mean patient age suggests that children were included. Ward et al. (21) included adolescents over the age of 12 yrs; however, they did not separately report the effects of the barbiturate therapy among the children. Ward et al. (21) reported that 54% of barbiturate-treated subjects developed hypotension—defined as a systolic blood pressure <80 mm Hg—compared with 7% of controls.

Refractory Intracranial Hypertension

Use of barbiturates to treat elevated ICP in children with severe head injury has been reported since the 1970s (22). Marshall et al. (22a) were the first to report that both control of ICP and outcome were improved with the use of barbiturates. Patient age was not specified in this report. In this case series, 25 patients with ICP >40 mm

Table 1. Evidence table

Reference	Description of Study	Data Class	Conclusion
Kasoff et al. (4), 1988	Case series of 21 children with severe TBI; 11 treated with pentobarbital for intractable ICP. Invasive hemodynamic monitoring used.	III	Children receiving high-dose barbiturates had decreased cardiac index and lower systemic vascular resistance; 91% required dopamine to maintain hemodynamic stability.
Pittman et al. (23), 1989	Case series of 27 children who received pentobarbital for ICP >20 mm Hg despite conventional care.	III	Fourteen of 27 achieved ICP <20 mm Hg with addition of pentobarbital. Seven of 27 experienced persistently elevated ICP, and three of those seven made good ultimate recovery.

TBI, traumatic brain injury; ICP, intracranial pressure.

Hg were treated with high-dose pentobarbital. When ICP was controlled, mortality rate was significantly reduced compared with patients with persistently elevated ICP (21% vs. 83%).

Kasoff et al. (4) reported a case series of 25 children with severe TBI. ICP was monitored in all patients, and surgically correctable lesions were treated with immediate operation. Pentobarbital was administered if ICP remained >20 mm Hg despite hyperventilation to P_{aCO_2} 25–30 torr and administration of dexamethasone and mannitol. Each patient ($n = 11$) who received pentobarbital was monitored with a pulmonary artery catheter. The clinical goals were to maintain ICP <20 mm Hg, cerebral perfusion pressure (CPP) >40 mm Hg, and hemodynamic stability. Ten of 11 children (91%) who received barbiturates required dopamine to maintain CPP compared with 11% of children who did not receive barbiturates. The authors state that all children who received barbiturates had diminished cardiac output and systemic vascular resistance. Nine of the children experienced hypotensive episodes despite intensive monitoring, fluid resuscitation, and dopamine infusions. Thirty-seven percent of the patients died. The specific effects of barbiturates on ICP and CPP were not reported.

Pittman et al. (23) reported a case series of 27 children with severe TBI who received pentobarbital for ICP >30 mm Hg if the intracranial hypertension failed to respond to other treatment modalities. Fourteen (52%) achieved ICP <20 mm Hg after addition of barbiturates. Six (22%) died within 48 hrs despite therapy, and seven had sustained elevation of ICP >35 mm Hg and reduction of CPP (<50 mm Hg) for several hours. No conclusions can be drawn from this study regarding the effect of pentobarbital-related reduction of intracranial hypertension on neurologic outcome. Three of seven patients with sustained elevation of ICP made good recoveries. The authors suggested that barbiturates may have a ben-

eficial effect on outcome even when refractory ICP is not controlled.

Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Eisenberg et al. (24) reported a multiple-center randomized clinical trial of high-dose barbiturates in severely head-injured patients with intractable ICP elevations. Patients were between the ages of 15 and 50 yrs. Information on children was not reported separately. This study is considered the best evidence for the use of high-dose barbiturates in adults with uncontrolled ICP. It is the primary study on which the adult guidelines for use of high-dose barbiturates are based (1).

Patients were randomly assigned to barbiturate therapy, whereas the control subjects continued to receive conventional therapies of hyperventilation, muscle relaxation, sedation, mannitol, and ventricular drainage (when possible). Successful control of ICP was the primary outcome variable. Patients in the control group could cross over to the barbiturate treatment group. Thirty-two percent of patients randomized to barbiturate therapy had control of ICP. ICP control was almost twice as likely to be achieved in barbiturate-treated patients compared with the conventional treatment group. The likelihood of survival among barbiturate responders at 1 month after injury was 92% compared with 17% among nonresponders. The primary cardiovascular complication was hypotension.

Therapeutic Regimens

A number of therapeutic regimens have been reported. Eisenberg et al. (24) used the following protocol for pentobarbital.

Loading dose: 10 mg/kg over 30 mins
Then 5 mg/kg every hour for three doses
Maintenance: 1 mg·kg⁻¹·hr⁻¹

Nordby and Nesbakken (25) reported on the use of thiopental in children and adults with severe TBI and used the following dosing regimen.

Loading dose 10–20 mg/kg

Maintenance: 3–5 ·kg⁻¹·hr⁻¹

Doses of thiopental were reduced if blood pressure decreased or ICP was <25 mm Hg.

Although the duration and optimal method to discontinue high-dose barbiturate administration have not been studied, often clinicians seek a period of 24 hrs during which there is good ICP control and no dangerous elevations before beginning to taper off the barbiturate infusion (26).

V. SUMMARY

Small studies of high-dose barbiturate therapy suggest that barbiturates are effective in lowering ICP in selected cases of refractory intracranial hypertension in children with severe TBI. However, studies on the effect of barbiturate therapy for uncontrolled ICP have not evaluated neurologic outcome. Use of barbiturates is associated with myocardial depression, increased risk of hypotension, and need for blood pressure support with intravascular fluids and inotropic infusions. Studies have not evaluated the effect of age on the risk of hemodynamic compromise during high-dose barbiturate therapy. The potential complications of high-dose barbiturate therapy in infants and children with severe TBI mandate that its use be limited to critical care providers and that appropriate systemic monitoring be used to avoid and rapidly treat hemodynamic instability.

There is no evidence to support use of barbiturates for the prophylactic neuroprotective effects or prevention of the development of intracranial hypertension in children with severe TBI.

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VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Clearly, a study of high-dose barbiturates for intractable ICP after severe TBI in children is needed to determine whether they improve outcome.
- The effect of barbiturate therapy in cases of diffuse cerebral swelling in children should be evaluated. Furthermore, no studies have reported the efficacy of high-dose barbiturates for intractable ICP in infants or after injury due to abusive head trauma.
- Age dependence of the deleterious hemodynamic effects of barbiturates deserves further study. Prolonged inhibition of synaptic activity in the developing brain during infancy has been shown to have deleterious effects in recent studies in laboratory models of brain injury (27).
- The effects of barbiturates in infants with severe TBI requires study.

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See APPENDIX on Next Page

APPENDIX: LITERATURE SEARCH STRATEGIES

SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

Chapter 13. Barbituates

1. exp craniocerebral trauma/
2. head injur\$.tw.
3. brain injur\$.tw.
4. 1 or 2 or 3
5. intracranial pressure/or "intracranial pressure" .mp.
6. intracranial hypertension/or "intracranial hypertension" .mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)