Evaluating the Therapeutic Response of Barbiturate Coma in Head Injury

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Abstract

INTRODUCTION

Patients with intracranial hypertension require immediate treatment to prevent neurophysiologic damage. It is estimated that 10-15% of patients with head injuries will manifest elevated ICP resistant to standard forms of treatment (sedation, paralysis, hyperventilation, hypothermia, cerebrospinal fluid drainage, osmotic diuretics, and surgery).[1,2] After conventional therapies have been optimized high-dose barbiturates may be administered. Barbiturates appear to exert their cerebral protective and ICP-lowering effects through several mechanisms: increasing cerebrovascular resistance and decreasing cerebral blood volume, decreasing cerebral metabolism, and acting as a free oxygen radical scavenger.[1,3] High-dose barbiturates for the management of elevated ICP remain controversial. The assessment of the therapeutic value of pentobarbital in patients with elevated ICP is difficult. Many of the trials are non-blinded, non-randomized, and lack comparable controls. In addition, it is difficult to make comparisons between these trials due to differences in conventional treatments used, measurements of outcomes, and doses of pentobarbital.[4,5,6,7,8] At this time, there are no clinical studies, which determine the most efficacious dosing regimen and method of monitoring pentobarbital for the treatment of elevated ICP.

MATERIALS AND METHODS

The objective of this study is to evaluate the relationship of pentobarbital loading doses to therapeutic levels and response. This is a retrospective chart review of patients admitted to an adult neurosurgical intensive care unit who received pentobarbital for the treatment of uncontrolled ICP between January 1, 1997 and December 31, 1998. Patients 18 years of age or older were included in the study if they received pentobarbital for the management of elevated ICP. They were excluded from the study if they received pentobarbital at an outside facility, did not have serum levels drawn or recorded, if the ICP was less than 20 mmHg at the initiation of pentobarbital, or if the charts were incomplete. Patients were identified from records in the Department of Pharmacy.

Patients were divided into four groups and compared according to the loading dose received (A= 15 mg/kg X 1, then 5 mg/kg X 3; B= > 15 mg/kg - < 30 mg/kg; C= 15 mg/kg; D= < 15 mg/kg). Dosing regimen A received a 15mg/kg bolus over 30 minutes followed by three 5mg/kg boluses over 15 minutes every hour. After the loading dose, a continuous infusion of 1.5 mg/kg/hr was initiated. Infusion rates were titrated to achieve a serum level of 30-40 mg/L and burst suppression on an electroencephalogram (EEG). Serum levels were drawn six hours after the end of the loading dose and every 12 hours afterwards. EEGs were performed approximately 12 hours after the end of the loading dose.

Data collection included: the mean time to achieve a therapeutic level of 30-40 mg/L, the mean time to achieve an ICP less than 20 mmHg, and the mean time to achieve burst suppression on an EEG. Other data which was evaluated included: loading and maintenance doses, serum levels with corresponding ICP and cerebral perfusion pressure (CPP), mortality, and APACHE II scores determined within 24 hours of admission to the ICU. Hemodynamic parameters (MAP; mean arterial pressure, ICP, and CPP) associated with the loading dose were monitored.

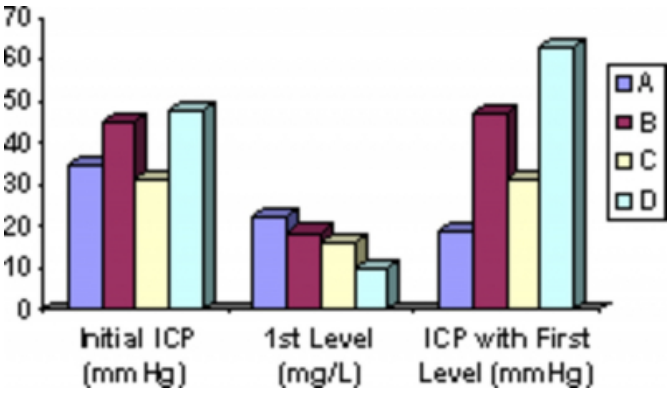
Statistical analysis was performed by one-way analysis of variance for mean ICP (serum level > 30 mg/L) versus loading dose regimen and Chi Square for mortality versus loading dose regimen.

RESULTS

Fifty-four patients were identified as receiving pentobarbital for the management of elevated ICP. Twenty-five patients were included in the analysis. The remaining patients were excluded for the following reasons: twelve charts were incomplete or missing, ten patients did not receive pentobarbital for six hours to have levels drawn, and seven patients had an ICP less than 20 mmHg at the initiation of pentobarbital. Of the 25 patients who met eligibility, 15 patients had closed head injuries secondary to trauma while ten patients experienced non-traumatic intracranial hemorrhages.

Figure 1

Graph 1: Comparison of ICP between Dosing Regimens



Dosing regimen A achieved a mean serum concentration of 22.3 mg/L and reduced the mean ICP by 12.7 mmHg at the time of the first serum level (graph 1). Dosing regimen A was the only dosing regimen, which decreased the ICP and MAP while increasing the CPP with the administration of the loading dose (table 2). Patients in dosing regimen A had the highest initial mean CPP (A; 79 ± 15 mmHg vs B; 61 ± 21mmHg, C; 56 ± 18 mmHg, and D; 49 ± 33 mmHg) when compared to the other dosing regimens.

Figure 2

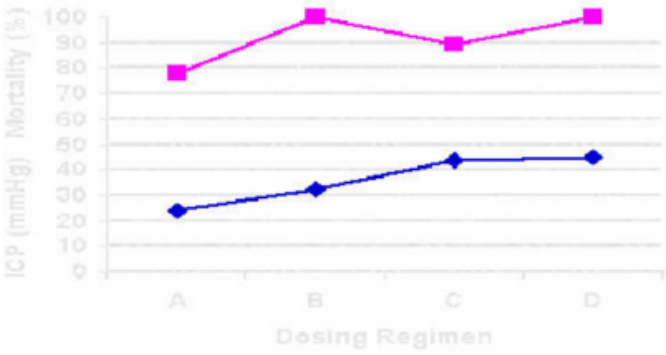
Table 2: Mean Hemodynamic Changes After the Loading Dose

Dosing Regimen	ICP (mmHg)	CPP (mmHg)	MAP (mmHg)
A (n = 9)	-16	+7.0	-8.5
B (n = 4)	+3.0	-1.6	-8.0
C (n = 9)	-5.0	-9.0	-1.5
D (n = 2)	NA	NA	NA

The mean time to achieve a barbiturate serum concentration greater than 30 mg/L was 29.4 ± 17.0 hours (13/25). Burst suppression, which was recorded in seven of the 25 patients, was achieved at serum concentrations less than 30 mg/L in 71% of the patients. The mean ICP when serum levels were greater than 30 mg/L was lowest in dosing regimen A when compared to other dosing regimens (p=NS). Mortality appears to be lower with higher loading dose regimens (p=NS) (graph 2).

Figure 3

Graph 2: Mean ICP (at serum level > 30 mg/L) and Mortality of Dosing Regimens



DISCUSSION

The assessment of the therapeutic value of pentobarbital for the treatment of elevated ICP is difficult. The majority of the literature is case reports. There are few randomized, blinded trials demonstrating pentobarbital's efficacy in lowering elevated ICP and improving outcome.4,5 In a series of 25 cases Marshall and colleagues evaluated the use of pentobarbital for the treatment of uncontrolled ICP in patients with severe head injuries.4 The initial pentobarbital loading dose (3-5 mg/kg) reduced the ICP in 76% of the patients. Prolonged pentobarbital infusions (not greater than 14 days) were associated with a reduction in the ICP to less than 15 mmHg in 13 patients. The mortality rate was 83% in the patients who did not respond to pentobarbital versus 23% in the patients who did respond.

In a multi-center, randomized trial Eisenberg and colleagues showed the chance of ICP control in patients randomized to pentobarbital was almost double that of patients who received conventional therapy.5 When the data was stratified for cardiovascular complications the advantage of barbiturate therapy increased to fourfold. In the majority of the cases, cardiovascular complications were hypotension defined as a systolic blood pressure less than 90 mmHg. When hypotension occurred both patient groups had an equal chance of success (62% vs 50%). The adverse effects of high-dose barbiturates are primarily related to the cardiovascular system.2,9 Hypotension can occur because of reduction in peripheral vascular smooth muscle tone and cardiac depression. Group A was the only dosing regimen, which decreased the ICP and MAP while increasing the

CPP.

It is assumed patients who received dosing regimen A were able to tolerate the decrease in ICP and MAP because they were more hemodynamically stable than the patients in the other dosing groups. Dosing regimen A had the highest initial mean CPP when compared to the other dosing regimens. It appears as though patients who were thought to be more hemodynamically stable received higher loading doses. Lower loading doses may have been given to patients with greater morbidity. Patients in dosing regimen D had the highest mean APACHE II score. However, two dosing protocols (dosing regimen A and C) were being utilized during this time. There may have been some confusion as to which protocol to administer.

Our study suggests there may be an association between the loading dose and ICP response which may lead to lower mortality. Hemodynamically stable patients appeared to receive higher loading doses which may have led to lower ICP and a reduction in mortality (graph 2). Nara and colleagues observed in a randomized study the ICP was significantly ($p < 0.05$) decreased and the CPP tended to be elevated as the pentobarbital dose increased.6 The findings of these two studies suggest in order to effectively reduce the ICP larger doses of pentobarbital should be administered.

There was an association between the loading dose, ICP response, and mortality; however, the sample size was too small to achieve statistical significance. Secondary to what has been observed in this study we have changed the pentobarbital loading dose in our protocol to 30 mg/kg over two hours. Patients in whom pentobarbital is to be administered are carefully selected and hemodynamic parameters are maximized before the initiation of the pentobarbital infusion. A prospective analysis of the changes made to the protocol is underway to determine if this association can be concluded.

CONCLUSION

There appears to be an association between loading dose and ICP response, which may lead to lower mortality. However, a larger sample size is required to make this determination.

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