JPPT | Single Center Retrospective Study

Enteral Pentobarbital in the Difficult to Sedate Critically Ill Children

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OBJECTIVE Difficult analgosedation is common and challenging in the pediatric intensive care unit (PICU). It is important to study alternative and supplemental sedatives for when the first-line agents become insufficient.

METHODS In this retrospective chart-review study, we report our center's experience in using intermittent doses of enteral pentobarbital as an adjunct sedative in 13 difficult to sedate critically ill and mechanically ventilated children. We compare the average sedation score and cumulative doses of other sedatives (opioids, benzodiazepines and alpha-2 agonists) in the 24 hours before and 24 hours after enteral pentobarbital initiation.

RESULTS The addition of enteral pentobarbital was associated with lower State Behavioral State (SBS) scores in 8 out of the 13 patients and on average smaller doses of opioids (decreased by 11%), benzodiazepines (BZD) (decreased by 5%) and alpha-agonists (decreased by 20%). No adverse effects were noted attributable to pentobarbital administration.

CONCLUSION Enteral pentobarbital seems to be safe and effective agent in the difficult to sedate critically ill child.

ABBREVIATIONS AE, adverse event; BZD, benzodiazepines; CAP-D, Cornell Assessment of Pediatric Delirium; PICU, pediatric intensive care unit; SBS, State Behavioral Scale; SE, status epilepticus.

KEYWORDS children; pediatric critical care; pediatric intensive care unit; pentobarbital; sedation.

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Introduction

Providing adequate sedation and analgesia to critically ill children on mechanical ventilation in the pediatric intensive care unit (PICU) is essential. Sedation and analgesia are needed for comfort, to decrease anxiety, to facilitate care, and to prevent self-harm.[1,2] Unlike adult patients, children rarely tolerate mechanical ventilation without sedation and analgesia.[2]

Several medications are recommended and commonly used to provide sedation in the PICU. Historically, opioids and benzodiazepines (BZD) were the first-line agents. The practice and recommendations have shifted over the last 2 decades with opioids and central alpha-2 receptor agonists as first-line agents. Benzodiazepines became less favorable due to high risk of developing delirium when used.[1–3]

Difficult analgosedation, while not well defined, is when large doses of the first-line sedatives become less effective.[1,2] This is reported in select patients early in the course of their illness for unknown reasons but more commonly with prolonged illness due to medication tolerance and tachyphylaxis.[1,2] Difficult analgosedation leads to undersedation and represents a real challenge to PICU staff.[1,4] Undersedation is associated with both physical and psychological risks like device dislodgment, unplanned extubation and delirium, and can lead to long-term consequences.[5] Additional available sedatives when the first-line agents become ineffective include propofol, ketamine, and inhaled anesthetics.[3] The use of those agents is both not well studied and associated with high adverse event rates.

Pentobarbital is a short-acting barbiturate commonly used in large doses as continuous infusion in refractory status epilepticus (SE) and refractory intracranial hypertension.[6] It is also used in small doses administered enterally in children undergoing sedated imaging procedures like magnetic resonance imaging and computed tomography scan.[7–12] When used in large doses, pentobarbital is associated with significant adverse events (AE) such as hemodynamic instability, infections, and ileus.[6] But when used in small doses, it has a favorable AE profile.[8,13] The use of pentobarbital administered enterally in small intermittent doses in mechanically ventilated children as an adjunct sedative has not been reported previously.

We report the use of intermittent enteral pentobarbital for 13 pediatric patients on mechanical ventilation

with difficult analgosedation exploring its effectiveness and safety as an adjunct sedative.

Methodology

We conducted a retrospective chart review of critically ill and mechanically ventilated children who received enteral pentobarbital in our PICU. Medical charts of selected patients were manually reviewed to collect the following data elements: patient demographics, discharge diagnoses, enteral pentobarbital doses with frequency in the first 24 hours of initiation, sedation level, delirium screening and treatments, cumulative doses of other sedatives (opioids, BZD, and alpha-2 agonists), hemodynamic parameters, and vasoactive medication use and fluid resuscitation in the 24 hours before and after the first dose of pentobarbital. The medical record was also reviewed for any reports of a new infection and antimicrobial use from the initiation of pentobarbital until discharge. Patients who received only 1 dose of pentobarbital, had received continuous infusion before the enteral doses, and those admitted with neurological illnesses were excluded.

At our institution, we use the State Behavioral Scale (SBS)[14] for sedation depth assessment and the Cornell Assessment of Pediatric Delirium (CAP-D) once a shift for delirium screening.[15] The SBS is recorded hourly. Both fentanyl and morphine were used for the patients in our cohort, so fentanyl doses were converted to morphine equivalents for easier comparison. Midazolam was the only BZD used in our cohort of patients; thus, no conversion was necessary.[16,17] We compared the average SBS in the 24 hours before and 24 hours after pentobarbital initiation at the patient level to assess for the pentobarbital effect on sedation depth.

A change in the other sedatives was considered increased or decreased if the cumulative dose in the 24 hours prior to the first dose of pentobarbital was 10% larger or smaller than the 24 hours after the first dose of pentobarbital, respectively.

Results

We identified 13 pediatric patients between the age of 2 months and 27 months admitted to our PICU from March 2018 through September 2020 and received enteral pentobarbital as an adjunct sedative while receiving mechanical ventilation (see Table).

While most of the patients received the first pentobarbital dose within 5 to 15 days of mechanical ventilation, some received it as early as the third day of mechanical ventilation. The dosage and frequency varied as noted in the Table. Dosing ranged from 2 to 4 mg/kg/dose and frequency ranged from 2 to 6 times per day. Dosing of enteral pentobarbital is not standardized in our institution, and thus the variability in dosing came from physician's preference and clinical judgment.

Table. Patient Characteristics, Enteral Pentobarbital Doses and the Change in the State Behavioral Scale

Case	Age (mo)	Gender	Primary Illness	MV Duration (days)	First Dose Day of MV	Number of Doses First 24 hr	Cumulative Dose /24 hr mg/kg	SBS Comparison*
1	3	M	Respiratory	9	6	2	9	Improved
2	20	M	Respiratory	6	2	3	12	Improved
3	2	M	Respiratory	39	29	3	15	Improved
4	12	F	Respiratory	6	3	2	4	Improved
5	20	M	Respiratory	9	6	4	16	Improved
6	5	F	Post-Operative	11	6	2	4	Worsened
7	12	M	Respiratory	4	2	9	30	Worsened
8	27	M	Cardiac	6	5	5	8	Improved
9	5	F	Respiratory	20	10	4	10	Worsened
10	3	M	Respiratory	25	15	3	13	Improved
11	15	M	Respiratory	7	3	6	12	unchanged
12	10	M	Respiratory	8	5	6	11	Improved
13	18	M	Respiratory	7	2	4	8	unchanged

F, female; M, male; MV, mechanical ventilation; SBS, State Behavioral Scale

* The SBS comparison is between the 24 hr prior to the first pentobarbital dose and the 24 hr after.

Eight patients had improvement in SBS scores within the first 24 hours of receiving enteral pentobarbital as an adjunct sedative, 2 patients had unchanged SBS, and 3 had worsening SBS scores.

Of the patients with improved SBS after enteral pentobarbital initiation, 4 required less cumulative doses of the other sedatives (opioids, BZD, and alpha-2 agonists), 2 required similar cumulative doses, and 2 required more. Age and total dose of pentobarbital did not seem to correlate with responsiveness.

On average, the use of all the other sedatives (opioids, BZD, and alpha-2 agonists) decreased after the addition of enteral pentobarbital in all 13 patients. The average decrease in opioid use was 11%, 5% for BZD, and 20% for alpha-2 agonists. None of the patients had hypotension requiring fluid resuscitation or vasoactive agents within the first 24 hours of pentobarbital initiation. None of the patients had a positive blood or urine culture, new reported infection, or were started on new antibiotics after pentobarbital was initiated.

Unfortunately, screening for delirium was scarce so the data is not presented. Only 1 patient was receiving pharmacological treatment for delirium when pentobarbital was started. No statistical analysis was performed.

Discussion

Difficult analgosedation is a common and challenging matter in caring for critically ill children.[1,2] Currently, PICU providers lack guidance on approaching the difficult to sedate child and have limited safe and effective alternatives to first-line agents.[1,2] In the last 2 decades, surviving a childhood critical illness has improved substantially, but this comes with longer PICU length of stay and duration of mechanical ventilation.[18] Hence, the search for safe and effective alternative sedatives is essential.

Large dose pentobarbital infusion is effective in treating both status epilepticus and intracranial hypertension but is usually reserved for refractory cases due to its high rate of complications.[6] Hypotension, respiratory depression, and respiratory infection are the most commonly reported AEs.[6]

On the other hand, the use of pentobarbital in procedural sedation has been shown to be effective and safe.[7–10] Enteral pentobarbital dose for procedural sedation is between 4 and 8 mg/kg in a single or divided doses[11] with reported complication rates of less than 1%.[11] Warden et al[9] reported 9796 sedations with enteral pentobarbital and a complication rate of 0.5%. While it seems to be slightly less effective in sedation than propofol, it is as effective as dexmedetomidine and chloral hydrate, and more effective than midazolam and etomidate.[7–10] Additionally, prolonged recovery, which is reported to be one of the downsides of enteral pentobarbital in procedural sedation, would be a desirable effect in mechanically ventilated patients.

With such a favorable efficacy and safety profile when used enterally in small doses, it is very reasonable to investigate whether intermittent enteral doses of pentobarbital in the PICU would be useful. It is important though to highlight that studies on enteral pentobarbital in procedural sedation reported better efficacy with children younger than 3 years of age[8,9] and that in our cohort all the patients were younger than 3 years of age. Although not all the patients in our cohort responded to enteral pentobarbital, a significant percentage of them demonstrated response and none of the patients had a AE.

Two studies reported the use of pentobarbital as a continuous infusion for sedation in the PICU. Tobias[19] reported 50 patients with difficult sedation for whom pentobarbital infusion was an effective alternative. Infusion was started at 1 mg/kg/hr and increased as needed. The infusion rate ranged from 1.2 +/− 0.4 mg/kg/hr on day 1 to 3.4 +/− 0.7 mg/kg/hr on day 5.[19] While some of the patients experienced mild withdrawal symptoms, there were no reported hemodynamic or other significant AE.[19] Yanay et al[20] reported the use of continuous infusion of pentobarbital in a smaller cohort (n = 8) of PICU patients with difficult sedation. They used larger initial doses than Tobias[19] and reported higher complications rate (initiation dose was 2.2 +/− 1 mg/kg/hr vs 1.2 +/− 0.4mg/kg/hr). Two patients became hypotensive, 1 patient developed erythema multiforme, and 1 patient developed a neuromuscular disorder. We believe most of the reported AEs associated with pentobarbital use are due to the larger doses and less likely to occur with small, intermittent doses. Our cohort while small, is larger than Yanay et al[20] cohort and yet we experienced no significant AE.

It is unclear why some of the patients did not respond positively. Delirium rather than undersedation is commonly the source of agitation.[21] Only 1 of the patients in our cohort was on pharmacological treatment for ICU delirium. Nevertheless, our results are promising for the use of enteral pentobarbital in critically ill children with difficult analgosedation. The response to enteral pentobarbital in procedural sedation is not uniform with reported cases of agitation when used for procedural sedation,[13,22] which can explain why some of our patients did not respond. It is also unknown whether the non-responders would have responded to larger doses. Even in otherwise healthy children undergoing nonpainful procedures, larger doses up to 8 mg/kg are commonly needed.[11]

Intermittent pentobarbital can be administered enterally or intravenously. Both routes provide similar efficacy, but the enteral route has longer duration of action and provides more stable serum concentrations, ensuring less fluctuation of sedation level.[23,24] Additionally, the intravenous route may be challenging if the patient has limited access and receiving multiple other intravenous medications. On the other hand, the

pharmacokinetics of enterally administered medication in critically ill patients can be unpredictable.[24] Poor enteral absorption in some critically ill patients may explain why some of the patients in our cohort did not respond to pentobarbital.

While further studies are needed to confirm our findings and better investigate the appropriate dosage, we believe that intermittent enteral pentobarbital can improve sedation in patients with early difficult sedation or when tolerance to first-line sedatives becomes an issue. We recommend a trial of enteral pentobarbital when large doses of first-line sedatives are inadequate for sedation and the patient has no signs of delirium or is already receiving treatment for delirium. Additionally, the use of intermittent enteral pentobarbital can spare the patients the use of larger cumulative doses of opioids and BZD.

Our study has a number of limitations, some of which are inherent to the retrospective nature of the study and the small sample size. As enteral pentobarbital use in mechanically ventilated patients has never been reported, we believe our data are worth reporting to guide future larger and prospective studies on the matter. Our study lacked adequate data on the delirium status of the patients which is an important factor when assessing difficult analgosedation. This is especially important as most of the cases in our cohort received continuous infusion BZD. Finally, investigating additive sedation in critically ill patients is challenging due to the high number of confounding factors like the changes in other medications (sedatives and non-sedatives), the change in the illness severity, and development/improvement of delirium.

Conclusion

The use of enteral pentobarbital in mechanically ventilated critically ill children with difficult analgosedation is potentially effective and safe. This study is the first report on using enteral pentobarbital for sedation in the PICU. Larger randomized controlled or observational trials with case matching are needed to further explore its safety across the different pediatric age groups, as well as the optimal dosage and timing.

Article Information

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Ethical Approval and Informed Consent. The authors asserted that enrolling parents and healthcare workers in the study comply with the standards and relevant national guidelines on human experimentation and have been approved by the institutional review board at the University of Missouri. All the participating parents, physicians and nurses provided written informed consent at enrollment.

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