Preliminary Report

Very High Dose Phenobarbital for Refractory Status Epilepticus

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Background: *Refractory status epilepticus (RSE), defined as status epilepticus that fails to respond to first, second and third-line therapy. The RSE is associated with high morbidity and mortality. Treatment guidelines of RSE give a spectrum of options, such as, continuous intravenous (i.v.) midazolam (MDL), or continuous i.v. propofol (PRO) as alternatives to phenobarbital (PB) or continuous i.v. pentobarbital (PTB).*
Objective: *To study the efficacy of very-high-dose phenobarbital (VHDPB) for treatment RSE.*
Study design: *Retrospective study.*
Material and Method: *The authors collected and analyzed data from adult patients who were diagnosed with RSE.*
Results: *The authors present 10 patients with RSE who were treated with VHDPB. All of them were generalized convulsive status epilepticus (GCSE). Ages ranged from 16-86 years old (mean: 43 years). PB dosage ranged 40-140 mg/kg/day (mean: 70 mg/kg/day). The duration of status epilepticus (SE) varied widely, ranged 1-44 days (mean: 7 days). PB level ranged 35.29-218.34 ug/mL (mean 88.1 ug/mL). RSE was controlled by VHDPB 70%, 30% were not controlled.*
Conclusion: *VHDPB were considered as alternative treatment for RSE.*

Keywords: *Refractory status epilepticus, Very high dose phenobarbital, Treatment*

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Status epilepticus (SE) is an emergency condition and contributes to a high mortality rate. SE defined as recurrent epileptic seizures without complete recovery between seizures. Generalized convulsive status epilepticus (GCSE) is the most common and most life-threatening form of SE[1]. Refractory status epilepticus (RSE), defined as SE that fails to respond to first, second and third-line therapy. The RSE is associated with high morbidity and mortality[2]. Treatment guidelines of RSE give a spectrum of options, such as, continuous intravenous (i.v.) midazolam (MDL)[3-5], or continuous i.v. propofol (PRO)[6,7] as alternatives to phenobarbital (PB) or continuous i.v. pentobarbital (PTB). However, in a survey of American neurologists, there was little agreement on third-and fourth-line therapy for RSE[2]. Claassen J, et al compared response, complications, and mortality in RSE patients treated with PRO, MDL, or PTB[2]. Forty-eight percent of the patients died, and mortality was not significantly associated with the choice of agent.

The ideal treatment of RSE should have several characteristics including effectiveness against

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many different seizure types, easy and safe handling and administration, lack of significant side effects in critically ill patients, and ease of monitoring. Crawford, et al reported very-high-dose phenobarbital (VHDPB) for RSE in 50 children [8], VHDPB controlled seizures in all cases. VHDPB has been easy and safe to use [8]. The authors present a series of patients with RSE in whom PB doses were titrated for seizures control without reference to predetermined maximum level or dose.

Material and Method

A retrospective study was conducted from January 1st, 1995 to December 31st, 2005 at the Department of Medicine, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand which is a university and referral hospital. The medical records of SE patients aged more than 14 years old. RSE is characterized by SE that fails to respond to first, second and third AEDs. The authors found 13 patients developed RSE, and 10 patients used VHDPB for control of RSE. PB dosage for RSE of 20 mg/kg intravenous, rate 50 mg/min and repeated the same dose every time of seizure attack.

Results

The authors identified 10 patients who used VHDPB for control RSE. Ages ranged from 16-86 years old (mean: 43 years). All of them were generalized convulsive status epilepticus (GCSE). The duration of SE varied widely, ranged 1-44 days (mean: 7 days). The aetiologies included: systemic lupus erythematosus (SLE) (2 cases), suspected herpes simplex encephalitis (HSE) (2 cases), hypoxic encephalopathy (2 cases), cerebral venous sinus thrombosis (CVST) (1 case), alcoholic withdrawal seizures (1 case) and unknown causes (2 cases).

Definite treatments were pulse methylprednisolone for SLE with central nervous system involvement, acyclovir for HSE, and low molecular weight heparin for CVST. All of the SE patients were treated with benzodiazepine (BZP) by intravenous injection, then phenytoin (PHT) loading by intravenous infusion. The mean duration between SE being diagnosed and anti-epileptic drug infusion; viz., BZP and PHT was 3.6 and 60.8 minutes, respectively, followed by VHDPB for all. The mean duration of seizures not controlled with PHT until controlled with VHDPB was 305.1 minutes.

PB dosage ranged 40-140 mg/kg/day (mean: 70 mg/kg/day). PB level ranged 35.29-218.34 ug/mL (mean 88.1 ug/mL). RSE was controlled by VHDPB 70%, 30% did not control. Seven patients were evaluated clinically and 4 by electroencephalography (EEG). The mean duration after seizures were controlled until consciousness was regained was 2.8 days. Complications from SE occurred in 10 patients, including: hospital-acquired pneumonia (10 cases), urinary tract infection (6 cases), and hypotension (5 cases but only one was a side-effect of VHDPB while four were due to septic shock), sepsis (4 cases), cardiac arrest (3 cases), and acute renal failure (2 cases).Three cases of RSE not controlled by VHDPB were controlled by PRO and PTB. Mean time of duration since admission to seizure stopped was 14.4 days.

During admission, 5 patients died from sepsis (100%) and renal failure (40%). Mean time of duration since admission to death was 8.5 days. Severe neurological deficits with total dependency were found in 4 patients. Only 1 patient had complete recovery. Mean of hospital stay in the survived group was 54 days. All of the patients were intubated with endotracheal tube. Half of them developed hypotension. However, refractory hypotension developed in only one patient. Home AEDs were PB and PHT. Mean dosage of PB was 192 mg/day and PHT was 323 mg/day.

Discussion

Treatments of RSE are i.v. MDL, PRO, PB, VHDPB, or PTB[6,7]. Moreover, nearly half of RSE died, and choice of AEDs did not effect the outcome[2]. VHDPB was easy and safe administration, and effectiveness. In addition, most Thai physicians are familiar with PB, and the cost is very cheap. The present study found 13 patients with RSE. Ten of 13 RSE patients were treated with VHDPB. Seven patients (70%) were controlled by VHDPB. Repeated doses of PB at 20 mg/kg/dose were then administered for recurrence of seizures, with a highest accumulated dose of 140 mg/kg/day.

Crawford et al reported the effectiveness of VHDPB without reference to predetermined maximum level or dose in controlling seizures in 50 infants and children[8]. Maximum dose administered within a 24-hour period was 120 mg/kg. Maximum serum level reported was 237 ug/mL (ranged 70-237, mean 110 ug/mL). Also the same finding as the present report; ranged 35.29-218.34; mean 88.1 ug/mL).

PB is many times more potent an anticonvulsant than PTB or thiopental when calculated to equal CNS depressant effects[9]. VHDPB can be useful in the care of patients with chronic RSE or refractory serial seizures, as it allows for time to control seizures while

other maintenance anticonvulsant changes are made. Drug interactions are not trivial, however, and seizures tend to recur during weaning. Depending upon the nature of the underlying disease, the clinical choice may be between long-term VHDPB and continued seizures. In some of these patients, the tendency for RSE diminishes with time, and VHDPB can be weaned accordingly.

The three main initial intravenous drug therapies for status epilepticus have been BZP, PHT, and PB. VHDPB has both practical and theoretic advantages over a higher dose of BZP or PHT for treatment of RSE. The use of high-dose BZP, unlike PB, is limited by acute functional tolerance to anticonvulsant effect and progressive resistance to additional doses. PB differs from PHT by having relatively linear and predictable volume of distribution and elimination kinetics. Any drug which is to be given repeatedly should have linear dosing and elimination kinetics and little or no acute tolerance to anticonvulsant effect.

Conclusion

VHDPB without a ceiling effect were considered as alternative treatment for RSE.

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ฟีโนบาร์บิทอลขนาดสูงมากในการรักษาภาวะชักต่อเนื่องชนิดดื้อต่อการรักษา

สมศักดิ์ เทียมเก่า, ณัฐกานต์ มยุรสาคร, ผานิต สุโข, สุทธิพันธ์ จิตพิมลมาศ, สุวรรณา อรุณพงค์ไพศาล, วรินทร พุทธรักษ์, ณรงค์ เอื้อวิชญาแพทย์, สุดา วรรณประสาท, ศิริพร เทียมเก่า, คัชรินทร์ ภูนิคม, อาภรณี ไชยาคำ, เจียมจิต แสงสุวรรณ

ภูมิหลัง: *ภาวะชักต่อเนื่องชนิดดื้อต่อการรักษาคือการชักชนิดต่อเนื่องที่ไม่ตอบสนองต่อการรักษาด้วยยากันชักชนิด 1, 2 และ 3 มีอัตราการเจ็บป่วยและเสียชีวิตสูง แนวทางปฏิบัติการรักษาภาวะดังกล่าวมีหลายทางเลือก ได้แก่ การให้ยาทางหลอดเลือดดำอย่างต่อเนื่อง มัยดาโซแลม พ็อพพอฟอล ฟีโนบาร์บิทอล เพ็นโทบาร์บิทอล*

วัตถุประสงค์: *เพื่อต้องการศึกษาถึงประสิทธิภาพของฟีโนบาร์บิทอลขนาดสูงมากในการรักษาภาวะชักต่อเนื่อง ชนิดดื้อต่อการรักษา*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลัง โดยการนำประวัติของผู้ป่วยที่วินิจฉัยเป็นภาวะชักต่อเนื่องมาศึกษา*

ผลการศึกษา: *พบผู้ป่วย 10 รายที่รักษาด้วยฟีโนบาร์บิทอลขนาดสูงมาก ผู้ป่วยทั้งหมดเป็นการชักชนิดเกร็งกระตุกทั้งตัว อายุระหว่าง 16 ถึง 86 ปี (ค่าเฉลี่ย 43 ปี) ขนาดยาฟีโนบาร์บิทอลระหว่าง 40-140 มิลลิกรัมต่อกิโลกรัมต่อวัน (ค่าเฉลี่ย 70 มิลลิกรัมต่อกิโลกรัมต่อวัน) ระยะเวลาการเกิดภาวะชักต่อเนื่องนาน 1-44 วัน (ค่าเฉลี่ย 7 วัน) ระดับยาฟีโนบาร์บิทอลระหว่าง 35.29-218.34 ไมโครกรัมต่อมิลลิลิตร (ค่าเฉลี่ย 88.1 ไมโครกรัมต่อมิลลิลิตร) ผลการรักษาร้อยละ 70 ตอบสนองต่อการรักษา และร้อยละ 30 ไม่ตอบสนองต่อการรักษา*

สรุป: *การรักษาด้วยฟีโนบาร์บิทอลขนาดสูงมากเป็นทางเลือกหนึ่งในการรักษาภาวะชักต่อเนื่องชนิดดื้อต่อการรักษา*