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Full Length Research Paper

Prolonged treatment with high-dose phenobarbital in patients suffering from acute encephalitis with refractory, repetitive partial seizures

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To investigate the safety and side effects of prolonged treatment with high-dose phenobarbital in patients suffering from acute encephalitis with refractory, repetitive partial seizures (AERRPS), 5 AERRPS patients meeting the Sakuma's criteria were recruited from July 2003 to September 2008. During the treatment with high-dose phenobarbital, the blood pressure, heart rate, cardiac rhythm, respiratory rate, blood gas, skin conditions, state of consciousness, pupil size, seizures and long-range electroencephalogram were monitored. After intravenous bolus injection of phenobarbital (200 mg) or intramuscular infection of phenobarbital for induction, and then phenobarbital was intravenously administrated at 1 to 1.5 mg/kg/h or intramuscularly given (200 mg) (or intravenous bolus injection) q 2 to 4 h to maintain plasma concentrations. The daily overall dose of phenobarbital was 1.2 to 2.4 g. The serum level of phenobarbital reached 100 µg/ml within 24 h and remained for 24 d to 100 d. Follow up was carried out for at least 6 months. During the treatment of high dose phenobarbital, these 5 patients were in coma and the scores of Glasgow coma scale were 3 to 5. The brainstem reflex was mostly preserved and the spontaneous breathing was absent. The side effects in the circulation system included arrhythmia and hypotension. Sinus tachycardia (n = 3) and ventricular/supraventricular tachycardia (n = 2) were controlled by amiodarone, and the blood pressure was decreased by 40 to 55/64 to 86 mmHg (n = 2) which resolved after dopamine treatment (5 to 10 µg/kg/min). Liver injury was evident and observed in all 5 patients. The serum levels of alanine aminotransferase, aspartate aminotransferase and γ glutamyl transferase was 57 to 385 IU/L, 38 to 365 IU/L and 54 to 542 IU/L, respectively. The maximal level of serum ammonia was 187 µg/dl. No yellow skin was observed, and the serum levels of direct and indirect bilirubin were normal. Skin reaction was mild and kidney function almost intact. When the serum level of phenobarbital was decreased to 50 µg/ml, the consciousness and spontaneous breathing recovered and side effects were nearly absent. It is indicated that severe side effects may occur during prolonged treatment with high-dose phenobarbital. When this strategy is necessary, assisted ventilation is recommended and side effects should be closely monitored.

Key words: Encephalitis, status epilepticus, phenobarbital, side effect, safety.

INTRODUCTION

The clinical manifestations and treatment of acute encephalitis with refractory, repetitive partial seizures (AERRPS) were first reported by Sakuma et al. (2001) in 2001 and has been considered as a new clinically defined syndrome. The long term status epilepticus and repetitive partial/systemic seizure are frequently un-responsive to traditional drugs for status epilepticus such as diazepam, valproic acid, phenytoin and lidocaine and treatment of this condition with high-dose anesthetics

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(midazolam and propofol) is still controversial (Yoshiaki et al., 2007). Under this condition, phenobarbital is preferable. The treatment of AERRPS with phenobarbital is characterized by high dose (>1.2 g/d), prolonged administration (from several weeks to several months), high serum level of Phenobarbital (about 100 µg/ml) and slow decrement of dose (Markowitz et al., 2011). Therefore, the serum level of Phenobarbital remains at a high level for a prolonged duration. In the present study, the side effects and safety of long term treatment of AERRPS with high-dose phenobarbital were evaluated in order to provide evidence for the safe and effective pharmacotherapy of AERRPS.

PATIENTS AND METHODS

A total of 29 inpatients with the age ranged from 13 to 55 years(mean 20±2.6 years) were recruited from the intensive care unit of the Department of Neurology, Affiliated Xuanwu Hospital of Capital Medical University from July 2003 to September 2008. The diagnosis of AERRPS was based on the criteria developed by Sakuma et al. 2001: (1) Partial seizures are interrupted with systemic seizures and the consciousness is absent; patients are un-responsive to high dose diazepam/valproic acid/phenytoin/lidocaine and require mechanical ventilation and treatment with high dose Phenobarbital. The administration of phenobarbital is long-lasting (several weeks to several months). (2) In the recovery stage and chronic persistent stage, the frequency of seizures is decreased but still higher than that in patients with epilepsy after encephalitis. Treatment with high dose phenobarbital is still required. (3) The cause of disease is unknown but the clinical manifestations are similar to those in encephalitis. In the present study, 5 patients (3 males and 2 females) were finally diagnosed as having AERRPS and the age ranged from 14 to 38 years. During the treatment with phenobarbital, the consciousness, pupil size, seizure, blood pressure, heart rate, cardiac rhythm, respiratory rate, blood gas, and skin condition were monitored, and routine urine and blood tests as well as detection of liver and kidney functions were performed. The total plasma protein, albumin and blood lipid were also measured and long range electroencephalograpgy (EEG) was also done. These patients were followed up for at least 6 months to observe the prognosis. The side effects of this treatment were recorded and analyzed, and as phenobarbital is the most effective anti-epileptic continuous state drug for encephalitis patients, but a large and long-term application of Phenobarbital would inevitably do harm to the patients, so we observed and summarized the risk in this study. Informed consent was obtained from the relatives of these patients.

Administration of phenobarbital

Once the patients were un-responsive to intravenous high dose diazepam, valproic acid and lidocaine and EEG showed extensive cerebral discharge (the first item in the criteria for AERRPS), intravenous bolus injection or intramuscular injection of phenobarbital (200 mg) was immediately done and the phenobarbital level remained by continuous intravenous injection at 1 to 1.5 mg/kg/h or intramuscular injection (intravenous bolus injection) (200 mg) q 2 to 4 h. The way in which phenobarbital was administrated was determined by the phenobarbital formulation: phenobarbital of powder formulation was used for continuous intravenous infusion or bolus injection and liquid formulation for intramuscular injection. The overall dose was 1.2 to 2.4 g daily which is 2 to 3 times higher than the upper limit. The serum phenobarbital level reached 100 µg/ml within 24 h and then remained (Yoshiaki et al., 2007). The high serum phenobarbital concentration maintained for 24 d to 100 d.

RESULTS

Clinical manifestations

Side effects of the nervous system

These patients remained in coma during the treatment and the score of Glasgow coma scale (GCS) was 3 to 5. The most severe patients had no response to any stimulation, and the mild patients had slight flexion following stimulation. The bilateral pupils had identical size: 2 mm in 1 patient and 3 to 5 mm in 4 patients; pupillary light reflex was compromised in 4 patients and one had no pupillary light reflex; no pinpoint pupils were observed. Two patients had no corneal reflex which was normal in the remaining 3 patients. Cough reflex was found in 3 patients and absent in 2 patients. The burst-suppression mode is not related to the dose of phenobarbital and serum phenobarbital level and determined by the individual sensitivity (Mirski et al., 1995). The burst-suppression mode in EEG is occasionally found in this kind of patients and its incidence relatively low. The serum phenobarbital of 100 µg/ml reached a toxic concentration which is life-threatening. Although the burst-suppression mode was not found, the existing relationship between serum Phenobarbital level and consciousness impairment was unequivocal.

Side effects of the respiratory system

The prevalence of respiratory suppression was extremely high and all patients required mechanical ventilation. These patients had respiratory failure as a result of inhibition of medullary respiratory center which was characterized by slow and shallow breathing as well as absence of spontaneous breathing in severe patients. At the early stage, the pulmonary function was favorable and the oxygenation index nearly normal. At the late stage, the pulmonary dysfunction was associated with the pulmonary infection following mechanical ventilation and subsequent consciousness impairment (Zhang et al., 2008). Once the infection was controlled, the oxygenation index returned to normal rapidly.

Side effects of the cardiovascular system

Side effects in the cardiovascular system were obvious. All patients had arrhythmia: sinus tachycardia in 3 patients (receiving no specific treatment) and

ventricular/supraventricular tachycardia in 2 patients, which were resolved after treatment with amiodarone of conventional dose. The blood pressure was decreased by 40 to 55/64 to 86 mmHg in 2 patients but the central venous pressure was normal, which was not related to the blood volume, and thus blood volume expansion was not required. The decrease of blood pressure might result from the suppression of the contraction of arterioles, which was resolved after administration of dopamine at 5 to 10 μg/kg/min.

These severe side effects were closely associated with the dose and serum concentration of Phenobarbital. When the daily dose of phenobarbital decreased to 0.4 to 0.6 g/d or the serum concentration of phenobarbital reduced to lower than 50 μg/ml, the symptoms of circulation system resolved and subsequent spontaneous breathing recovered, and the mechanical ventilation was successfully discontinued. The consciousness recovery was later than the breathing recovery, but more complete.

Skin side effects

Three patients had systemic rashes which were red, recurrent and related to the skin hypersensitivity to Phenobarbital. Severe skin side effects such as Steven-Johnson syndrome were not found.

Imbalance of fluid and electrolytes

The incidence of imbalance of fluid and electrolytes was relatively low and found in only 1 patient who developed syndrome of inappropriate antidiuretic hormone secretion characterized by mild edema and dilutional hyponatremia. This condition was associated with several factors: nervous system diseases; positive pressure ventilation; severe pulmonary infection and difficult to be determined as side effects of phenobarbital treatment.

Laboratory examinations

Routine blood test

The white blood cell count was normal or mildly increased at the early stage, and reduced to 3.8×109/L in one patient at the late stage without clinical significance. The platelet count was initially normal but mildly decreased (81 to 92×109/L) in 2 patients during the treatment among whom 1 had mild hemorrhage and subcutaneous ecchymosis following medical procedure and no treatment was performed. The bleeding time, clotting time and coagulation function were normal. At the early stage, the red blood cell count and hemoglobin were in normal range and 3 patients had mild anemia (80 to 100 g/L) at the later stage.

Blood biochemistry

The total protein remained normal and hypoalbuminemia (2.4 to 2.8 g/dl) was noted in 3 patients, which may be related to the acute stress, fever, status epilepticus and nutrition supply and cannot completely be attributed to the side effects of phenobarbital. The cholesterol, triglyceride, low density lipoprotein and high density lipoprotein remained nearly normal during the treatment and the kidney function was intact. The liver function was severely impaired. All patients had liver dysfunction of different extents. The alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ glutamyl transferase (γ-GT) were 57 to 385, 38 to 365 and 54 to 542 IU/L. The maximal level of serum ammonia was 187 μg/dl. The levels of direct and indirect bilirubin were normal. After administration of reduced glutathione, these parameters were slightly improved. When the dose of Phenobarbital decreased to 0.4 to 0.6 g/d or the serum level of 0.4 to 0.6g/d reduced to lower than 50 μg/ml, the ALT and AST returned to normal or were slightly increased, and serum ammonia was in normal range. The γ-GT was abnormal for a long time (more than one year) but only mildly or intermediately increased.

Prognosis

All patients survived through the study but residual neurological impairment was observed. One was at a low state of consciousness, 3 had psychomotor disturbance of different degrees and 1 had residual seizure with favorable recovery. The outcome of these patients was related to AERRPS itself and we could not confirm that the outcome was secondary to the side effects of phenobarbital treatment (Table 1).

DISCUSSION

Since phenobarbital was introduced into clinical practice, it has been a first line antiepileptic and sedative drug and widely applied in the treatment of seizures and status epilepticus and for sedation. Pre-operative medication of phenobarbital, antiepileptic treatment with phenobarbital and pre-examination sedation accounts for 42, 36 and 8% of cases, respectively. In addition, about 2% of patients with viral encephalitis, intrahepatic cholestasis, frequent vomiting, prevention of post-operative seizures, recurrent seizures in muggy syndrome or neonatal pneumonia experience the treatment with phenobarbital. The medication of phenobarbital for longer than 30 d accounts for only 8% of side effects which are mainly found in short term application of phenobarbital (Sun et

Table 1. Side effects of long term treatment with high-dose phenobarbital in AERRPS patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	14	15	18	17	38
Gender	Female	Female	Male	Male	Male
Phenobarbital treatment					
Duration (d)	24	30	28	100	42
Maintenance dose (g/d)	1.2	1.6	1.8	1.8	2.4
Maximal level (μg/ml)	98	101	96	108	134
Clinical manifestations					
GCS score	3	4	3	5	3
Pupil size (mm)	3	2	4	5	4
Light reflex	Yes	Yes	Yes	No	Yes
Corneal reflex	No	Yes	Yes	No	Yes
Cough reflex	Yes	No	Yes	No	Yes
Spontaneous breathing	No	No	No	No	No
Cardiac rhythm	Ventricular tachycardia	Sinus tachycardia	Sinus tachycardia	Sinus tachycardia	Supraventricular tachycardia
Blood pressure	Normal	Normal	Hypothension	Normal	Hypothension
ALT peak (IU/L)	254	57	385	165	108
AST peak (IU/L)	184	38	238	365	112
γ-GT peak (IU/L)	384	54	542	245	98
Ammonia peak (μg/dl)	142	98	187	165	144
EEG					
Attack	Extensive attack	Extensive attack	Extensive attack	Extensive attack	Extensive attack
Interval	slow-wave, spike-wave	slow-wave, spike-wave	low-amplitude slow wave	fast and slow wave/ spike-wave	fast and slow wave/ spike-wave
Prognosis	unable to study; clumsy movement	unable to study; favorable movement	Favorable; lack of self-sustaining	low state of consciousness	psychomotor disturbance

al., 2005). Yang et al. (1998) monitored the serum level of phenobarbital in 4367 patients, but only 1.9% of patients had the phenobarbital concentration of higher than 40 μg/ml. Furthermore, the side effects in this study were not related to the maximal serum level of phenobarbital. Luo et al. (2005) reported phenobarbital ata dose of 1.2 to 2.2 g/d was safe for patients with status epilepticus but the serum concentration of phenobarbital was not monitored. The side effects and safety of long term treatment with phenobarbital of high dose have not been reported previously. In the present study, based on the pathophysiological characteristics of AERRPS patients, phenobarbital of high dose was used and high serum concentration of phenobarbital was prolonged (Sakuma et al., 2001; Yoshiaki et al., 2007; Awaya et al., 2007), and our results showed this strategy was safe and feasible. No burst-suppression mode was observed in EEG, which was not consistent with previously reported by Yoshiaki et al. (2007). In the study of Yoshiaki et al. (2007), burst - suppression mode was found in 1 of 3 patients when the phenobarbital was administered at 5 mg/kg/h and the serum phenobarbital level was 145 μg/ml. Our results were similar to a study reported in Tainwan in 2008 (Shyu et al., 2008).

The side effects of phenobarbital involve several systems including nervous system, skin, respiratory system, blood system, genitourinary system and circulation system. Sun et al. (2005) reported all the life-threatening side effects of phenobarbital in the skin: Steven-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis, which finally resulted in secondary multiple organ failure and death. The side effects in the nervous system include toxic encephalopathy, seizure, seizure deterioration, etc. In the present study, manifestations of the skin were mild and these patients mainly manifested central suppression induced coma, respiratory failure, arrhythmia, decrease of blood pressure and other symptoms due to circulatory system disorders. Prolonged high serum level of phenobarbital (100 μg/ml) may significantly suppress the central nervous system (mainly cortical inhibition) resulting in phenobarbital coma which was severe (GCS

scale of 3 to 5). The brainstem function was suppressed and characterized by the inhibition of the respiratory center resulting in absence of spontaneous breathing. The suppression of the circulation center is not evident and the side effects of phenobarbital in circulation system include mild arrhythmia and mild decrease of blood pressure which respond to conventional treatments. These findings suggest the bulbar function was not completely suppressed and the inhibition of circulation function is indirect, but not caused by suppression of central systems. The pupil size was moderately enlarged and light reflex was still present. The corneal reflex, conjunctival reflex and cough reflex were partially preserved, and the suppression of midbrain and pons was relatively mild. In addition, the suppression of central nervous system is reversible. When the dose of phenobarbital decreases to conventional level or the serum level of phenobarbital returns to <50 μg/ml, the consciousness and breathing completely recover spontaneously.

The liver impairment was obvious and characterized by significant increase of ALT, AST, γ-GT and ammonia. However, hepatic coma was not observed. Except for γ-GT, the remaining parameters returned to normal once the dose of phenobarbital decreased. The recovery of γ-GT was long-lasting. Moreover, the bilirubin, blood lipids and total plasma protein remained at a normal level.

All these patients survived but residual neurological impairment was observed which was associated with AERRPS itself (Yoshiaki et al., 2007). Prolonged phenobarbital may lead to abnormal intelligence, abnormal behaviors and psychology or ataxia but motor system remains intact (Ou et al., 2005). The relationship between these conditions and prolonged phenobarbital cannot be confirmed. On the contrary, when the status epilepticus in AERRPS patients cannot be controlled by phenobarbital and further treatment with anesthetics is controversial (Shyu et al., 2008), long term application of muscle relaxants is recommended but the side effects of this strategy is difficult to predict. Furthermore, muscle relaxants mainly block the neuromuscular junction and are used to control the intramuscular twitch. Therefore, these drugs cannot control the discharge of cerebral neurons and are not effective for seizure.

Conclusion

Taken together, the prolonged high-dose phenobarbital is feasible and safe for the treatment of status epilepticus in AERRPS and a life-saving strategy. This strategy has obvious but reversible suppression of consciousness and respiratory. During the treatment with high dose phenobarbital, mechanical ventilation is recommended and side effects should be closely monitored, which assures the safe application of phenobarbital.

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