

## High dose phenobarbitone for status epilepticus in adults

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### Abstract

**Objective:** To assess the efficacy of high dose phenobarbitone in status epilepticus. **Methods:** Status epilepticus was defined as more than 30 minutes of (a) continuous seizure activity or (b) two or more seizures without recovery of consciousness in between. The study period was from January 1994 to January 1997. Intravenous (IV) phenobarbitone up to a maximum of 20 mg/kg body weight was given if seizures continued after maximal doses of diazepam (20 mg) and phenytoin (30 mg/kg). Subsequent phenobarbitone was given in 100 mg at hourly intervals till burst suppression was achieved. The duration of burst suppression ranged from 5-7 days. Patients who continued to have seizures despite having received one gram of phenytoin and phenobarbitone were included in this analysis. **Results:** There were 14 patients in this study. The age range was 15-76 years. The underlying causes were: viral encephalitis (6), remote symptomatic epilepsy (2), brain abscess (1), and anticonvulsant non-compliance (5). Nine patients (64%) developed hypotension (Bp <100/60), and pressors were required in eight. Serum phenobarbitone levels ranged from 26.5 mg/l to 307.5 mg/l (mean 120.3 mg/l). Two patients died as a consequence of the underlying illness whereas one perished from refractory hypotension secondary to barbiturate therapy. The long term outcome were: good (5), poor (5), died (3), lost to follow up (1). Outcome was dependent on age, duration of time prior to institution of barbiturate coma and refractory nature of seizures. **Conclusion:** High dose phenobarbitone was effective in termination of all cases of status epilepticus when no limits are imposed upon the maximum dose. Hypotension was a common complication, frequently requiring vasopressor therapy. The mortality was 21% with equal number of the survivors having good versus poor outcome.

**Key words:** Status epilepticus, phenobarbitone, barbiturate coma

### INTRODUCTION

Status epilepticus (SE) is a neurological emergency with a high morbidity and mortality. It is defined as more than 30 minutes of (a) continuous seizure activity or (b) two or more seizures without recovery of consciousness in between.<sup>1,2,3</sup> It presents either as generalised convulsive seizures, non-convulsive status or repeated partial seizures. Adult onset status epilepticus without a history of epilepsy is usually due to an underlying disorder. These include infections of the central nervous system and cerebrovascular accidents. Prompt recognition and aggressive management is needed. Patients require a succession of intravenous (IV) medications such as diazepam, phenytoin and phenobarbitone. There has been only rare reports of high dose phenobarbitone in resistant cases of SE where no ceiling is imposed on the maximum dose of phenobarbitone.<sup>4,5</sup> This is the report of a study using high dose IV phenobarbitone in SE in the Tan Tock Seng Hospital, Singapore. The patients were from a 3-year period from January

1994 to January 1997. Prior to September 1995, patient records were retrospectively reviewed. Beginning October 1995, the study was prospective.

### METHODS

All patients with SE were admitted to the Neuro-Intensive Care Unit. Initial management included resuscitation, and identification and treatment of precipitating factors. Venous blood was drawn for anti-convulsant level and metabolic screening. IV diazepam 10 mg ( up to a maximum of 20 mg ) was followed by loading of IV phenytoin at 20 mg/kg body weight if status epilepticus was not aborted. If seizures continued, an additional 5 mg/kg body weight phenytoin was given, up to a maximum dose of 30 mg/kg body weight.<sup>1,3</sup> Patients with persistent seizures were given an IV phenobarbitone infusion of 300 mg at a rate no faster than 100 mg/min. Mechanical ventilation was instituted before further doses could be administered because of the risk of respiratory depression caused by

phenobarbitone. If seizures continued, additional phenobarbitone was given, up to a maximum of 20 mg/kg body weight.<sup>1</sup> Subsequently, phenobarbitone was given in 100 mg boluses at hourly intervals until a burst suppression pattern on electroencephalogram was achieved, or hypotension precluded further administration. Patients were kept in burst suppression for two to seven days<sup>2,6,7</sup>, after which the maintenance dosage of IV phenobarbitone infusion was reduced periodically to determine if the drug had induced a remission. If status epilepticus recurred on the electroencephalogram, the phenobarbitone dosage was increased and patients maintained in burst suppression for an additional forty-eight to seventy-two hours. Persistent hypotension required fluid challenge and vasopressor therapy with IV dopamine and adrenaline. A central venous line was inserted and euvolemia was maintained. Total anti-convulsant dosages in each twenty-four hour period was recorded and serum levels were obtained one hour after drug dosing. High dose phenobarbitone is defined as any dose higher than the standard loading dose of 20 mg/kg. Only patients who continued to have refractory

seizures despite loading of one gram phenytoin and phenobarbitone were included in this study.

## RESULTS

### *Patient characteristics*

There were 14 patients in this study. Their ages ranged from 15-76 years with a mean of 46 years. The male to female ratio was 6 : 8. With regards to aetiology, there were 6 patients (43%) with viral encephalitis and 2 with remote symptomatic epilepsy from previous cerebrovascular disease. SE was precipitated by sepsis from urinary tract infection and bronchopneumonia in these 2 patients. One patient had a brain abscess and 5 patients (36%) were non-compliant to anticonvulsants. Of the later, 4 had cerebral palsy with mental retardation while the fifth had a recurrent meningioma after resection.

With regards to the type of seizure, 6 (43%) were complex partial seizure while 8 (57%) were generalised tonic-clonic seizure (Table 1).

Six patients (43%) had previous seizures whereas SE was the first manifestation of seizure in 8 patients (57%). In the former group, 4 had

**TABLE 1: Seizure characteristics of 14 patients**

Pat no.	Age yrs	Sex	Etiology	Previous seizure	Seizure type	Initial seizure	Intercurrent seizure	Outcome
1	59	M	Viral encephalitis	N	GTC	Y	N	G
2	66	F	Viral encephalitis	N	GTC	Y	N	B
3	51	M	Viral encephalitis	N	GTC	Y	N	G
4	50	M	Viral encephalitis	N	CPS (NC)	Y	N	D
5	73	F	Viral encephalitis	N	GTC	Y	N	L
6	69	F	Viral encephalitis	N	GTC	Y	N	G
7	40	M	Remote symptomatic	Y	CPS (NC)	N	Y	D
8	39	F	Remote symptomatic	N	GTC	Y	Y	G
9	53	M	Brain abscess	N	CPS (NC)	Y	N	B
10	76	F	Non compliance	Y	CPS (C)	N	Y	G
11	15	F	Non compliance	Y	CPS (C)	N	Y	B
12	31	M	Non compliance	Y	GTC	N	Y	B
13	34	F	Non compliance	Y	CPS (C)	N	Y	B
14	40	F	Non compliance	Y	GTC	N	Y	D

M = Male, F = Female, Y = Yes, N = No, GTC = Generalized tonic-clonic seizure, CPS = Complex partial seizure, NC = Non-convulsive, C = Convulsive, G = Good, B = Bad, L = Lost to follow-up, D = Deceased.

cerebral palsy, one had a previous stroke, and another had a recurrent meningioma. In the later group, central nervous system infections were the most important underlying causes: 6 had viral encephalitis and one had brain abscess.

All patients had brain imaging either with computed axial tomography (CT) or magnetic resonance imaging (MRI). Of 6 patients with encephalitis, two had diffuse cerebral oedema on CT while four had a normal CT. All patients with remote symptomatic epilepsy had cortical infarcts. In patients with cerebral palsy, CT was either normal or showed focal brain atrophy. CT showed a left frontal lobe abscess in one patient.

Six patients had lumbar puncture performed for suspected brain infection. Of the 6 patients with encephalitis, the cell count ranged from 1-16 with a predominant lymphocyte count. Total protein ranged from less than 0.4 g/l to 0.82 g/l. Glucose was normal. Cerebrospinal fluid viral (herpes simplex and enteroviruses), bacterial, fungal and tuberculous cultures as well as serology for herpes simplex virus were negative in all patients.

#### *Course of treatment and results*

The mean duration before institution of barbiturate coma was 4.5 days (4-10). The mean cumulative phenobarbitone dosage was 5.39 gm (1.06-20). Nine patients (64%) developed hypotension (Bp <100/60), mostly during initial loading. IV dopamine and adrenaline were necessary in 8. One patient responded to fluid challenge only.

The mean duration to seizure control was 7.2 days (4-20). The mean duration of burst suppression was 4.5 days (2-7). There was a wide range of serum phenobarbitone levels achieved during burst suppression (26.5-307.5 mg/l). The mean level was 120.3 mg/l. When the phenobarbitone dosages were reduced, the patients became alert and conscious at mean serum phenobarbitone level of 48.0 mg/l (38.2-62.1). The patients were successfully extubated at mean phenobarbitone level of 48.5 mg/l (23.9-78.6).

#### *Outcome*

There were 3 in-patient mortality (21%). The causes of death were bronchopneumonia, hypoxic encephalopathy and refractory hypotension (phenobarbitone level of 307.5 mg/l). Ten of the surviving patients and their relatives were personally interviewed 1-3 years after the SE. One patient was lost to

follow-up. The outcome was divided into good or poor, based on the ability to return to previous employment, independence in activities of daily living (ADL) and recurrent seizures.<sup>8,9</sup> It was poor when patients could not return to their former jobs and/or their cognitive handicap required them to seek assistance in ADL. It was good when they were able to return to their original employment, although they were frequently less adept than before. No formal neuro-psychological tests were conducted. The outcome was: Good: 5 patients (36%); poor: 5 patients (36%); mortality: 3 patients (21%); lost to follow-up: 1 patient (7%). The occupations of the 5 patients with good outcome were: company executive (2), grocery shop owner (1), housewife (1) and errand boy (1). The occupations of the 5 patients with poor outcome were: unemployed with cerebral palsy (2), office worker (2), housewife (1). All the 5 patients with poor outcome had impairment of memory, attention-span and concentration.

The followings were possible prognostic factors for poor outcome: (a) Advanced age: the mean age was 52 years for the 5 patients with poor outcome as compared to the average of 46 years; (b) Longer duration before institution of barbiturate coma: the mean was 5.6 days compared to the average of 4.5 days; (c) The more refractory seizures: the SE required an average of 8 days to terminate as compared to the average of 7.2 days; the mean burst suppression duration was 5.3 days as compared to the average of 4.5 days; the cumulative phenobarbitone dosage was 6.5 g compared to the average of 5.4 g. On the other hand, the underlying aetiologies did not appear to be important.

#### **DISCUSSION**

SE is associated with a high morbidity and mortality and should be aggressively managed. The underlying aetiology should also be quickly identified and promptly treated. In our study, the most common underlying aetiologies were central nervous system infections (50%) and non-compliance to anti-convulsants (36%).

IV diazepam, phenytoin and phenobarbitone are among the commonly used drugs in SE. The main disadvantage of IV phenobarbitone is its relatively slow time to reach peak brain concentrations (approximately 30 minutes after IV infusion), although seizure control is achieved within 10-15 minutes. This contrasts with IV diazepam which enters the brain within 10

seconds and IV phenytoin which reaches peak brain concentrations in 15 minutes.

However, there are many advantages in the use of IV phenobarbitone. The half-life of the drug is long (50-150 hours) and there is absence of acute tolerance, a marked contrast to the benzodiazepines. Unlike phenytoin, there is relatively linear dosing and elimination kinetics. There is tolerance to sedative effects with the anti-convulsant effect at a much lower dosage than the respiratory depressant effect. This was due to the aryl drug moiety which conveyed potent anticonvulsant properties at doses below values that depress the brainstem reticular formation and consciousness. The higher therapeutic index allowed non-anaesthetic doses of the drug to be effective. It is also many times more potent an anticonvulsant than pentobarbitone or thiopentone at equivalent central nervous system depressant effects. This is attributed to its preferential concentration in active epileptiform cortical regions and specific physico-chemical membrane-stabilising action. It is also potentially cerebro-protective.<sup>10</sup> In distinction to short and medium half-life barbiturates or inhalational anaesthesia, high dose phenobarbitone is an extension of a usual initial treatment for SE.

The main reason for high dose phenobarbitone not being commonly used in SE is the fear of causing respiratory depression and hypotension, especially during loading. The latter is a hazard at high serum levels or when levels are rapidly rising. Shaner et al<sup>3</sup> reported an incidence of hypotension of 11% and Crawford et al<sup>4</sup> 10%. In the latter study, vasopressor therapy was needed in 80% of hypotensive patients. In both studies, hypotension was easily controlled. These findings differ markedly from our incidence of hypotension of 64%, with one mortality. Pressor treatment was required in 8 out of 9 patients. However, the short and medium half life barbiturates and inhalational anaesthetics are also associated with a common occurrence of hypotension.<sup>4,7</sup>

Crawford et al<sup>4</sup> retrospectively reviewed 48 children with 50 episodes of refractory SE treated with very-high-dose of phenobarbitone. They found that it controlled seizures in all cases when no limits were imposed upon maximum dosage. Serum phenobarbitone levels ranged from 70 to 344 mg/l. The only other study employing high dose phenobarbitone was a case report by Mirski et al<sup>5</sup> of a patient with refractory SE concurrently treated with pentobarbital, phenobarbitone and phenytoin. In that patient,

serum phenobarbitone levels of 220-290 mg/l were reached with daily phenobarbitone requirements of 2.5-3 g. Hemodynamic support with vasopressors was only briefly required. Our study with all patients responding to high dose phenobarbitone confirm that it is an effective therapy for SE. The phenobarbitone blood level at 26.5-307.5 mg/l also correspond to that of Crawford et al.<sup>4</sup>

The mortality rate in this study was 21%. Two patients died as a consequence of their underlying illness while one as complication of therapy. For the survivors, the outcome was equally distributed in "good" and "poor" categories. This is not surprising in view of the severity of the underlying disease and the refractory nature of the seizures.<sup>8,9</sup> Crawford et al<sup>4</sup> reported a mortality of 18%, with 60% having severe neurological impairments in his series of cases.

There remains much uncertainty in the use of barbiturate coma for the treatment of SE. The optimal duration for maintenance of burst suppression and interburst intervals is unknown. The recommended duration of barbiturate anaesthesia ranged from 12 hours to 13 days, and the interburst intervals from two to thirty seconds from different authors.<sup>2,6,7,10</sup> We maintained the burst suppression pattern for a mean period of 4.5 days and kept the interburst interval at 5 to 10 seconds.

In conclusion, high dose phenobarbitone is effective in treating refractory SE. The potential benefits of high dose phenobarbitone should be balanced against the common complication of hypotension. The mortality is high and neurological sequel is common reflecting the severity of the underlying disease.

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