Original article

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Mega-dose phenobarbital therapy for super-refractory status epilepticus

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ABSTRACT – *Aims*. To evaluate the efficacy and safety of mega-dose phenobarbital (MDPB; enteral or parenteral phenobarbital >10 mg/kg/day) for treating super-refractory status epilepticus (SRSE; continuous or recurrent status epilepticus for ≥24 hours after the onset of continuous anaesthetic treatment) in adult patients.
Methods. Adult patients with SRSE who were treated with MDPB in our institution from March 2005 to September 2014 were reviewed. We collected data on basic demographics, clinical features, functional status, anticonvulsant treatment, and possible adverse events. SRSE outcome was divided into six categories: successful therapy, initial failure, breakthrough seizures, withdrawal seizures, intolerable side effects, and death during treatment.
Results. Ten adult patients with SRSE received MDPB. Median age at seizure onset was 38 years (range: 18-59), and half were male. All patients had no history of seizures and had symptoms suggestive of viral encephalitis. Median duration of status epilepticus was 17.5 days (range: 6-60) and anaesthetics were used for a median of 14.0 days (range: 2-54) before MDPB. Successful control of SRSE was achieved in half of the patients, however, only one of ten patients was able to fully recover at discharge. Median duration of the MDPB was 45.5 days and the maximum serum phenobarbital level reached a median of 151.5 μg/ml. Patients with successful MDPB therapy had normal brain imaging (80% vs. 0%; p=0.048) and better functional outcome at discharge and after three months of follow-up. Infection was the most critical complication, along with cardiorespiratory depression.
Conclusion. MDPB is a therapeutic option for control of SRSE when other choices are exhausted.

Key words: super-refractory status epilepticus, mega-dose phenobarbital, management, outcome

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Status epilepticus (SE) is a life-threatening neurological emergency that requires prompt treatment with antiepileptic drugs (AEDs). In 30-40% of cases, SE persists despite the use of several anticonvulsants and requires treatment with general anaesthetics; this is referred to as refractory SE (RSE) (Lowenstein and Alldredge, 1998; Brophy *et al*., 2012). Super-refractory SE (SRSE) is defined as RSE that continues for ≥24 hours after the use of general anaesthetic medication, including cases in which the SE recurs with reduction or withdrawal of anaesthesia (Ferlisi and Shorvon, 2012). Patients with SRSE have high morbidity and mortality (Holtkamp *et al*., 2005; Cooper *et al*., 2009).

Treatments for SRSE are often based on clinical reports and expert opinion. To date, a variety of treatments for SRSE have been proposed: general anaesthetics, AEDs, a ketogenic diet, hypothermia, electroconvulsive therapy, and vagal nerve stimulation (Ferlisi and Shorvon, 2012). Each treatment for SRSE has its advantages and disadvantages, but most are not easily accessible and are accompanied by a high risk of severe adverse events (Cooper *et al*., 2009; Shorvon, 2011a).

Phenobarbital (PB) is cited in a number of guidelines for treatment of SE in adults (10-20 mg/kg) and in children (10-15 mg/kg) (Shorvon, 2011b; Brodie and Kwan, 2012). Often, a higher dose of PB is necessary to control refractory SE. We used the term "mega-dose phenobarbital" (MDPB) to define enteral or parenteral PB ≥10 mg/kg without reference to a maximum level or dose (Crawford *et al*., 1988). MDPB has often been used to control RSE in paediatric (Crawford *et al*., 1988; Wilmshurst *et al*., 2010) and adult patients (ADILTS, 1999; Wang *et al*., 2011; Tiamkao *et al*., 2013). However, only a few case reports have described MDPB treatment in adult patients with SRSE (Mirski *et al*., 1995; Bausell *et al*., 2011). The aim of this study was to evaluate efficacy and safety of MDPB for treating SRSE in adult patients. In this study, very-high-dose phenobarbital is referred to as MDPB.

Materials and methods

Study population

The primary question was whether MDPB could control SRSE in adult patients. After this study was approved by the Institutional Review Board of Seoul National University Hospital, we screened for patients in this hospital with a serum level >60 μg/ml of PB by reviewing laboratory data from March 2005 to September 2014, to find possible cases of MDPB therapy. We reviewed the medical records of the patients to identify those who received MDPB for SRSE. SRSE was defined as continuous or recurrent SE for ≥24 hours after the onset of continuous anaesthetic treatment (*i.e*. high-dose benzodiazepines, barbiturates, propofol, or ketamine) (Shorvon and Ferlisi, 2011).

Clinical data

We conducted a comprehensive review of medical records and all possible clinical data for patients who met the criteria. Collected data included basic demographics, history of seizures, SRSE aetiology, seizure type, duration, and severity using the Status Epilepticus Severity Score (STESS) (Rossetti *et al*., 2008). The Glasgow Coma Scale (GCS) and modified Rankin Scale (mRS) were scored to evaluate the level of consciousness and functional status on admission and at MDPB initiation. Neuroimaging (MRI, or if not possible, computed tomography) and EEG data obtained during hospitalisation (including data obtained from studies performed at admission and at MDPB initiation) were reviewed.

Convulsive seizure was defined as seizure with any focal or generalized motor activity witnessed by medical staff; non-convulsive seizures were defined as EEG seizures (rhythmic discharges with evolution in frequency, location, or morphology; simple PLEDS were not included) without any motor activity (Cooper *et al*., 2009). The duration of SE and use of AEDs and anaesthetic agents before MDPB were reviewed. MDPB treatment duration, maximum 24-hour cumulative dose, maximum serum PB level, and complications that may be related to MDPB were also recorded.

Clinical outcomes

The outcome of SRSE was divided into six categories, as described previously (Ferlisi and Shorvon, 2012): successful therapy, initial failure, breakthrough seizures, withdrawal seizures, intolerable side effects, and death during treatment. SE control was defined when ictal activity ceased on EEG for >48 hours with or without consciousness (Pugin *et al*., 2014). Recurrence of SE during MDPB therapy was defined as breakthrough seizures, and SE recurrence during or within 48 hours after tapering of MDPB was defined as withdrawal seizures (Ferlisi and Shorvon, 2012; Pugin *et al*., 2014). Additional outcome measures included length of stay in hospital and ICU, number of AEDs, and GCS and mRS score at discharge. Additional follow-up information recorded GCS and mRS score, and seizure frequency at three months after discharge.

Statistical analysis

Data are expressed as the median, range, and SD for continuous variables, and as counts (percentages) for

categorical variables. We compared the demographic and clinical data of patients who achieved successful therapy with MDPB with those of patients who failed MDPB treatment. Continuous data were compared using a Mann-Whitney *U* test, and a Fischer exact *t* test was used for categorical data. Significance was set at $p<0.05$.

Results

Clinical features and demographics

We identified 26 patients with a serum level of PB in excess of 60 μg/ml. Sixteen patients were excluded from analysis: six patients were in RSE without any use of IV anaesthetics; four patients were not in status epilepticus, but were treated with MDPB for recurrent intractable seizures; three patients received PB from another hospital and information regarding its dose and duration was not available; and three other patients were treated with a usual PB dose, and the maximum serum level barely reached above 60. Ultimately, 10 adult patients with SRSE who were treated with MDPB were included in our analysis (*figure 1*).

Median age at seizure onset was 38 years (range: 18-59) and 50% were male. The patients were previously healthy, and none had seizures or were exposed to AEDs. All patients had symptoms or signs suggestive of viral encephalitis, and eight of ten patients had non-specific prodrome lasting for 2-15 days before seizure onset. CSF pleocytosis was seen in six of the patients with a median white blood cell count of 22 (range: 6-73). All had epileptiform discharges on EEG and half of the patients showed either mesial temporal lesion or cortical swelling on MRI. However, extensive infectious screening including viral polymerase chain reaction and CSF cultures were negative. Detailed demographics and clinical characteristics of the patients are described in *supplementary table 1*.

Six patients had both convulsive and non-convulsive seizures during SRSE, and four other patients presented only convulsive seizures. Median STESS score was 3.5 (range: 2-4). Median duration of SE was 17.5 days (range: 6-60) and anaesthetics were used for a median of 14.0 days (range: 2-54) before MDPB. A median of two (range: 1-3) anaesthetics were used, either as a single agent or in combination: midazolam (9/10), thiopental (5/10), pentobarbital (2/10), ketamine (2/10), and propofol (1/10). In addition to IV anaesthetic drugs, a median of four (range: 2-5) AEDs were used in combination: levetiracetam (6/10), phenytoin (6/10), topiramate (6/10), oxcarbazepine (4/10), valproic acid (4/10), PB (4/10), carbamazepine (2/10), clobazam (2/10), and pregabalin (1/10). Median mRS and GCS scores at admission were 5 (range: 4-5) and 3.5 (range: 3-10), respectively (*table 1*).

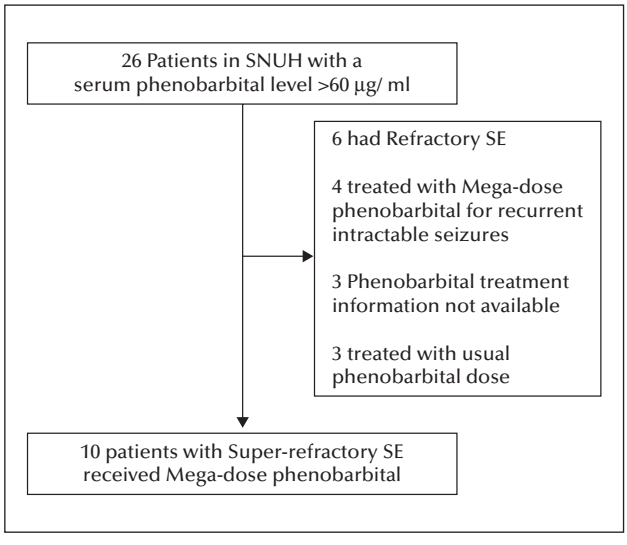

Figure 1. Study profile.
SNUH: Seoul National University Hospital; SE: status epilepticus.

MDPB treatment

MDPB was continued for a median of 45.5 days (range: 11-84). The median maximum cumulative 24-hour dose of PB was 38.6 mg/kg/day (range: 18-95.7), and the maximum measured PB serum level reached a median of 151.5 μg/ml (range: 82.2-353.7). At the time of MDPB initiation, EEG showed electrographic seizures in four patients, generalized periodic discharges in three, and burst suppression in the other three patients. A median loading dose of 25 mg/kg (10-40) was administered at MDPB initiation, and was repeated if necessary. MDPB was initiated after withdrawal of anaesthetics in five patients, and five others commenced MDPB during anaesthetic coma therapy. Four of the 10 patients had been taking the usual dose of PB with a median serum level of 50.8 μg/ml (20.6-62.7) before MDPB (*table 2*).

Systemic infection occurred in all of the patients during SRSE, including pneumonia (5/10), urinary tract infection (4/10), fungal infection (2/10), and line infection (2/10), either alone or in combination. Three of the patients had sepsis following a fungal infection (Patients 7 and 10) or bacterial pneumonia (Patient 8). All patients were intubated before MDPB during IV anaesthesia, and had a subsequent tracheostomy for respiratory support. Eight of 10 patients were able to be weaned from a ventilator, with a median PB level of 81.3 μg/ml (range: 24.0-124.6). Seven patients developed hypotension that required a median of two (range: 1-2) vasopressor agents (four patients before MDPB). Other complications included ileus (4/10), elevated liver enzymes (3/10), pseudomembranous colitis (1/10), atelectasis (1/10), and rhabdomyolysis (1/10).

Table 1. Demographics and seizure characteristics of patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age at seizure onset	23	20	27	38	45	59	39	18	38	57
Sex	M	M	F	F	F	M	F	M	M	F
Admission mRS/GCS	5/3	5/3	4/5	5/4	5/3	5/10	5/3	5/4	4/3	5/4
Type of seizure (convulsive/ non-convulsive)	Both	Both	Both	Con-vulsive	Both	Con-vulsive	Con-vulsive	Con-vulsive	Both	Both
STESS	2	4	3	4	4	3	4	3	3	4
Duration of SE* (days)	35	6	19	19	16	7	15	60	46	8
Duration of anaesthetics* (days)	31	5	16	5	14	4	14	54	36	2
No. of anaesthetics*	2	1	2	2	2	1	3	2	2	2
No. of AEDs*	4	5	3	3	2	4	4	4	4	4

Abbreviations: M: Male; F: Female; STESS: Status Epilepticus Severity Score; mRS: modified Rankin Scale; GCS: Glasgow Coma Scale; SE: status epilepticus; AED: antiepileptic drug; MDPB: megadose phenobarbital; *before MDPB.

Table 2. Mega-dose phenobarbital treatment.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Total length of MDPB (days)	14	45	24	19	84	11	46	60	59	53
Maximum 24-hr cumulative dose (mg/kg/day)	29.5	60.2	30	18	30	95.7	73.1	36.8	40.4	88.2
Maximum serum level (μg/ml)	82.2	174	111	>80, exact level not checked	116.9	314.6	195.8	115.8	151.5	353.7
Number of AEDs during MDPB	5	5	2	3	3	4	3	2	6	5
Number of vasopressors used	2	0	2	1	2	1	2	0	0	2

Abbreviations: MDPB: megadose phenobarbital; AED: antiepileptic drug.

Outcome of MDPB treatment

Successful therapy was achieved for five of the ten patients with MDPB, one died during treatment, two had withdrawal seizures, and the other two had initial MDPB failure. SE was initially controlled in eight patients after a median of 24.5 days (range: 6-41) use of MDPB, five of whom achieved successful outcome (the clinical course of one patient [Patient 2] is described in *supplementary figure 1A*). MDPB therapy was eventually unsuccessful for three patients. One died of septic shock during MDPB (Patient 7; *supplementary figure 1B*), and two others had withdrawal seizures during PB tapering; PB was tapered off too rapidly in one patient after achieving seizure control (Patient 6; *supplementary figure 1C*) and sepsis developed during PB tapering and triggered SE recurrence in another patient (Patient 7). In the remaining two patients, MDPB initially failed to control SRSE and other treatments were required including hypothermia and immunotherapy (Patients 9 and 10; Patient 9 is described in *supplementary figure 1D*). Five of the patients who commenced MDPB during anaesthetic coma therapy were able to be weaned off anaesthetics after a median of four days (range: 2-12) after MDPB.

The median ICU and hospital length of stay was 50 days (range: 18-292) and 86 days (range: 54-384), respectively. The median number of AEDs prescribed at discharge was four (range: 3-7), and six of seven living patients were on a median of 5 mg/kg/day (range: 2-23) PB at discharge. On discharge, median mRS and GCS scores were 5 (range: 1-6) and 4.5 (range: 3-15), respectively. More than half of the patients with successful MDPB treatment had a GCS score $\geq$10. Three patients died during hospitalization because of multiorgan failure following sepsis; one died of septic shock during MDPB maintenance, one month after initial SE control, and the other two patients developed fungal sepsis subsequent to MDPB treatment.

At three months after discharge, five of the seven living patients were available for follow-up. Four of the patients with successful MDPB therapy had intermittent partial seizures once or twice a week. One patient who initially had unsuccessful MDPB was still unresponsive with two complex partial seizures per day. Median mRS and GCS scores of the patients were 4 (range: 2-5) and 15 (range: 5-15), respectively (*table 3*). Detailed information regarding MDPB treatment and outcome is described in *supplementary table 2*.

Patients with successful MDPB therapy had normal brain imaging (80% vs. 0%, p=0.048), and had a better level of consciousness and functional status at discharge (median GCS: 10 vs. 3, p=0.005; median mRS: 4 vs. 6, p=0.022) and after three months of follow-up (median GCS: 15 vs. 3, p=0.015; median mRS: 3 vs. 6, p=0.032). The MDPB therapy failure group was treated with a higher cumulative 24-hour dose of PB (median: 30 vs. 73.1, p=0.028) and tended to have a higher maximum serum PB level (median: 114.0 vs. 195.8, p=0.086). Successful MDPB therapy was not associated with age (p=0.295), SE severity (p=0.817), or duration of SE (p=0.917) (*table 4*).

Discussion

We report 10 adult patients with SRSE who were treated with MDPB (PB dose >10 mg/kg/day). SRSE was initially controlled in eight patients within a median of 24.5 days after initiating MDPB, and five of them achieved successful therapy with MDPB. MDPB may therefore be a therapeutic option to control SRSE, when other choices are exhausted.

Cryptogenic new-onset refractory status epilepticus (NORSE) describes a group of previously healthy adults who present with refractory prolonged SE without known aetiology (Gall *et al*., 2013; Wilder-Smith *et al*., 2005), as in our patients. Patients with NORSE have prodromal symptoms before SE and often are suspected to have viral encephalitis (Bausell *et al*., 2011). Accumulating evidence supports that autoimmune aetiology may be the underlying cause of NORSE, and immunotherapy may bring about better outcome (Gall *et al*., 2013). However, only three of our patients were screened for neuronal autoantibodies, and immunotherapy was attempted in four with no clear benefit. More extensive immunological studies may have revealed underlying aetiologies in our patients.

A high dose of PB is necessary to control severe SRSE. Prolonged SE induces synaptic $GABA_A$-receptor trafficking and reduces the density of functional GABA receptors in synapses (Naylor *et al*., 2005; Goodkin *et al*., 2007). GABA receptor modification results in pharmacoresistance to barbiturates and the usual dose of PB will be less effective in SRSE. Higher doses of PB could be beneficial in SRSE because PB has no anticonvulsant ceiling effect.

The effect of a high dose of PB to control RSE has been reported. The first large study was a retrospective review of 48 children with RSE treated with very-high-dose phenobarbital (Crawford *et al*., 1988), with all except one achieving successful therapy with a maximum dose of 120 mg/kg/day and a serum level of 344 μg/ml. MDPB at a maximum dose of 80-140 mg/kg/day was used to treat adult patients with RSE in several case series (ADILTS, 1999; Tiamkao *et al*., 2013), and SE was controlled in 50-70% of the patients with significant mortality (17%-50%). To our knowledge, only a small number of case reports of MDPB treatment in SRSE have been reported to date. Three children with SRSE received 80 mg/kg/day PB for several months and all achieved SE control

Table 3. Seizure control and outcome.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Seizure outcome	Successful therapy	Successful therapy	Successful therapy	Successful therapy	Successful therapy	Withdrawal seizure	Withdrawal seizures	Death during treatment	Initial treatment failure	Initial treatment failure
Days to wean anaesthetics after MDPB	0	0	0	12	4	0	6	0	2	4
Days to initial SE control	20	41	31	15	11	6	30	29	N/A	N/A
ICU length of stay (days)	24	30	90	33	58	57	292	18	46	54
Length of hospitalization (days)	73	165	99	68	384	58	292	62	154	54
No. of AEDs at discharge	5	7	3	4	4	4	N/A	N/A	7	N/A
PB dose at discharge (mg/kg)	0	10	4	1.8	4.5	22.9	N/A	N/A	5.5	N/A
Discharge mRS/GCS	3/14	4/10	5/6	1/15	5/6	5/3	6/3	6/3	5/3	6/3
Disposition	Rehabilitation facility	Rehabilitation facility	Nursing home	Home	Nursing home	Other hospital	Death (fungaemia, sepsis)	Death (septic shock)	Nursing home	Death (fungaemia, sepsis)
Follow-up										
Seizure frequency at 3 months after discharge	1 CPS/week	1 CPS/week	N/A	1 SPS/week	2 SPS/week	N/A	N/A	N/A	2 CPS/day	N/A
mRS/GCS at 3 months	2/15	4/15	N/A	1/15	5/11	N/A	6/3	6/3	5/5	6/3

Abbreviations: N/A: not applicable; SE: status epilepticus; MDPB: megadose phenobarbital; ICU: intensive care unit; AED: antiepileptic drug; PB: phenobarbital; mRS: modified Rankin Scale; GCS: Glasgow Coma Scale; CPS: complex partial seizure; SPS: simple partial seizure

Table 4. Characteristics of patients with successful mega-dose phenobarbital therapy.

	Total	Successful MDPB therapy (*n*=5)	MDPB failure (*n*=5)	*p* value
Age at seizure onset (years)	38 (18-59)	27 (20-45)	39 (18-59)	0.295
Male sex (%)	5 (50.0)	3 (60.0)	2 (40.0)	1
GCS at admission	3.5 (3-10)	3.0 (3-5)	4 (3-10)	0.572
mRS at admission	5 (1-6)	5 (4-5)	5 (4-5)	1
STESS	3.5 (2-4)	4.0 (2-4)	3.0 (3-4)	0.817
Imaging abnormality	6 (60.0)	1 (20.0)	5 (100.0)	0.048
Duration of SE before MDPB (days)	17.5 (6-60)	19.0 (6-35)	15.0 (7-60)	0.917
Maximum 24-hr cumulative PB dose (mg/kg/day)	38.6 (18-95.7)	30 (18.0-60.2)	73.1 (36.8-95.7)	0.028
Maximum serum PB level (μg/ml)	151.5 (82.2-353.7)	114.0 (82.2-174.0)	195.8 (115.8-353.7)	0.086
Total length of MDPB (days)	45.5 (11-84)	24 (14-84)	53.0 (11-60)	0.465
ICU length of stay (days)	50 (18-292)	33.0 (24-90)	54.0 (18-292)	0.754
Length of hospitalization (days)	86 (54-384)	99 (68-384)	62.0 (54-292)	0.310
GCS at discharge	4.5 (3-15)	10 (6-15)	3 (3-3)	0.005
mRS at discharge	5 (1-6)	4 (1-5)	6 (5-6)	0.022
GCS at 3 months	8 (3-15), *n*=8	15 (11-15), *n*=4	3 (3-5), *n*=4	0.015
mRS at 3 months	5 (1-6), *n*=8	3 (1-5), *n*=4	6 (5-6), *n*=4	0.032

Abbreviations: SE: status epilepticus; MDPB: megadose phenobarbital; mRS: modified Rankin Scale; GCS: Glasgow Coma Scale; STESS: Status Epilepticus Severity Score; ICU: intensive care unit.

(Lee *et al*., 2006). Two cases of adult patients with SRSE treated with a maximum of 1,400-3,000 mg MDPB (maximum serum level: 151.5-290 μg/ml) along with anaesthetics have also been reported (Mirski *et al*., 1995, Bausell *et al*., 2011). Although accompanied by many complications, including septic shock and cardiorespiratory depression, the patients were able to overcome SRSE after several months of treatment. Details of the studies are summarized in *supplementary table 3*.

In our study, the dose of PB was increased up to 96.1 mg/kg/day to control SRSE with a maximum serum level reaching 353.7 μg/ml, which is comparable to other reports. Because PB shows a higher therapeutic index as an anticonvulsant relative to barbiturate anaesthetics (pentobarbital or thiopental) (Mirski *et al*., 1995), MDPB may have some benefit over general anaesthetics in controlling SRSE. In five of our patients, MDPB initially controlled SRSE after replacing general anaesthetics that failed to resolve SE. Successful treatment of SRSE with MDPB was associated with normal neuroimaging findings, which is consistent with a previous report (Osorio and Reed, 1989). Aggressive treatment with MDPB could be used especially for those with normal brain imaging. Those with unsuccessful MDPB treatment received a higher dose of PB and had a higher serum PB level. The PB dose and serum level escalated because SRSE continued despite MDPB treatment and so a higher dose was administered to control the SE.

SRSE is known to be associated with poor functional outcome. (Shorvon, 2011a). Of note, despite control of SRSE by MDPB, only one patient was able to fully recover and return home at discharge. Others had sequelae after SRSE and required rehabilitation or had to be transferred to a nursing home or other hospital. However, those with successful SRSE control had better functional outcome at three months, with a median mRS of 3. Good functional outcome can occur even after SRSE, and therefore premature withdrawal of care should be avoided (Shorvon, 2011a). Aggressive treatment including MDPB can be used to control SRSE for better long-term functional outcome.

The high rate of complications following MDPB has always been a drawback of its clinical use. Its side effects include haemodynamic instability, immunosuppression, and reduced gastrointestinal motility, which can limit the dose and the duration of MDPB use (Robakis and Hirsch, 2006). Previous studies have focused on the respiratory and circulatory depression effect of PB (Crawford *et al*., 1988; ADILTS, 1999; Lee *et al*., 2006). All patients in our study required assisted ventilation, and seven patients required a median number of two vasopressors to control low blood pressure. However, these complications were well managed and reversed during ICU care. Respiratory depression of PB is tolerable for a relatively short time and patients can maintain self-respiration at a high level of PB (Mirski *et al*., 1995). In our series, patients were able to regain spontaneous breathing even at a serum level >60 μg/ml of phenobarbital, and some patients were able to maintain stable blood pressure without any vasopressors even with a PB dose of over 27 mg/kg/day and a serum level exceeding 150 μg/ml.

Infection was the most critical complication during MDPB treatment. PB is known to increase the risk of immunosuppression by inhibiting phagocytosis by leukocytes and lymphocyte activation (Neuwelt *et al*., 1982; Humar *et al*., 2004). All of the patients in our study had an in-hospital infection, and three died of sepsis during MDPB. Mortality was 30% in our series, which is comparable to previous reports regarding SRSE (Holtkamp *et al*., 2005; Cooper *et al*., 2009). However, it is important to note that all mortality in the current study was the result of sepsis. During MDPB therapy, close observation for signs of infection is essential, with prompt and aggressive treatment as required.

Interpretation of this study should be made in light of its limitations. Although so far the largest case series of SRSE in patients treated with MDPB, our study included only 10 patients with SRSE. It was also a retrospective single-centre study, which might have resulted in selection bias. Indeed, all patients included in this study had cryptogenic new-onset RSE, which is often associated with poor outcome (Shorvon, 2011a). Because MDPB was used without reference to a predetermined maximum level or dose, the dosage schedule varied among the patients. Moreover, because the use of other AEDs and other interventions including immunotherapy was not controlled, we cannot exclude the possibility that other treatments led to control of SE.

Conclusion

This study suggests that MDPB therapy can be used as a treatment option to control SRSE. Half of the patients successfully overcame SRSE and were able to regain awareness. Because a high complication rate accompanies MDPB, one should be alert to the possible side effects and manage them promptly. The selection of patients who can benefit from aggressive MDPB, such as patients with normal brain imaging, may be vital in successful SRSE treatment. In conclusion, MDPB can be a useful therapeutic option to control SRSE when other choices are exhausted. □

Supplementary data.
Summary didactic slides and supplementary tables and figures are available on the www.epilepticdisorders.com website.

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References

ADILTS HDPFSEI. High dose phenobarbitone for status epilepticus in adults. *Neurol Asia* 1999; 4: 25-9.

Bausell R, Svoronos A, Lennihan L, Hirsch LJ. Recovery after severe refractory status epilepticus and 4 months of coma. *Neurology* 2011; 77: 1494-5.

Brodie MJ, Kwan P. Current position of phenobarbital in epilepsy and its future. *Epilepsia* 2012; 53(8): 40-6.

Brophy GM, Bell R, Claassen J, *et al*. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012; 17: 3-23.

Cooper AD, Britton JW, Rabinstein AA. Functional and cognitive outcome in prolonged refractory status epilepticus. *Arch Neurol* 2009; 66: 1505-9.

Crawford TO, Mitchell WG, Fishman LS, Snodgrass SR. Very-high-dose phenobarbital for refractory status epilepticus in children. *Neurology* 1988; 38: 1035-40.

Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain* 2012; 135: 2314-28.

Gall CRE, Jumma O, Mohanraj R. Five cases of new onset refractory status epilepticus (NORSE) syndrome: outcomes with early immunotherapy. *Seizure* 2013; 22: 217-20.

Goodkin HP, Sun C, Yeh JL, Mangan PS, Kapur J. GABA(A) receptor internalization during seizures. *Epilepsia* 2007; 48(5): 109-13.

Holtkamp M, Othman J, Buchheim K, Masuhr F, Schielke E, Meierkord H. A "malignant" variant of status epilepticus. *Arch Neurol* 2005; 62: 1428-31.

Humar M, Pischke SE, Loop T, *et al*. Barbiturates directly inhibit the calmodulin/calcineurin complex: a novel mechanism of inhibition of nuclear factor of activated T cells. *Mol Pharmacol* 2004; 65: 350-61.

Lee WK, Liu KT, Young BW. Very-high-dose phenobarbital for childhood refractory status epilepticus. *Ped Neurol* 2006; 34: 63-5.

Lowenstein DH, Alldredge BK. Status epilepticus. *New Eng J Med* 1998; 338: 970-6.

Mirski MA, Williams MA, Hanley DF. Prolonged pentobarbital and phenobarbital coma for refractory generalized status epilepticus. *Crit Care Med* 1995; 23: 400-4.

Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neuroscience* 2005; 25: 7724-33.

Neuwelt EA, Kikuchi K, Hill SA, Lipsky P, Frenkel E. Barbiturate inhibition of lymphocyte function. *J Neurosurgery* 1982; 56: 254-9.

Osorio I, Reed RC. Treatment of refractory generalized tonic-clonic status epilepticus with pentobarbital anesthesia after high-dose phenytoin. *Epilepsia* 1989; 30: 464-71.

Pugin D, Foreman B, De Marchis G, *et al*. Is pentobarbital safe and efficacious in the treatment of super-refractory status epilepticus: a cohort study. *Crit Care* 2014; 18: R103.

Robakis TK, Hirsch LJ. Literature review, case report, and expert discussion of prolonged refractory status epilepticus. *Neurocrit Care* 2006; 4: 35-46.

Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008; 255: 1561-6.

Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. *Epilepsia* 2011a; 52(8): 53-6.

Shorvon S. The treatment of status epilepticus. *Curr Opin Neurol* 2011b; 24: 165-70.

Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011; 134: 2802-18.

Tiamkao S, Suttapan K, Pranbul S, Tiamkao S, Sawanyawisuth K. Adjunctive enteral phenobarbital for adult status epilepticus: a brief report. *Neuropsychiatr Dis Treat* 2013; 9: 1829-34.

Wang L, Qi X, Gao R. Prolonged treatment with high-dose phenobarbital in patients suffering from acute encephalitis with refractory, repetitive partial seizures. *Scientific Research and Essays* 2011; 6: 4259-63.

Wilder-Smith EP, Lim EC, Teoh HL, *et al*. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. *Ann Acad Med Singapore* 2005; 34: 417-20.

Wilmshurst JM, van der Walt JS, Ackermann S, Karlsson MO, Blockman M. Rescue therapy with high-dose oral phenobarbitone loading for refractory status epilepticus. *J Paediatr Child Health* 2010; 46: 17-22.

TEST YOURSELF

(1) What is the definition of super-refractory status epilepticus?

(2) Patients with prolonged status epilepticus are often resistant to usual doses of barbiturates. What is the underlying mechanism for the pharmacoresistence?

(3) What was the most critical complication following mega-dose phenobarbital therapy, and what is the underlying mechanism?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".