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Research Article

Is Phenytoin or Fosphenytoin Still Useful in Treating Refractory Status Epilepticus? A Case Series

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Abstract

Objective: The objective of this study was to perform a retrospective analysis of the management of status epilepticus at Tufts Medical Center to determine the utility of phenytoin and fosphenytoin as an anti-epileptic medication in status epilepticus (SE) and refractory status epilepticus (RSE). The efficacy of phenytoin and fosphenytoin as a first-line therapy, or after multiple AEDs were attempted, was also investigated. This study attempts to evaluate the role phenytoin or fosphenytoin may continue to play as part of a multi-drug regimen for the management of status epilepticus.

Background: Status epilepticus is a neurological emergency caused by continuous epileptic activity that can last from minutes to days. Timely and effective management of these seizures is essential in the treatment of these patients. In tandem with benzodiazepines, phenytoin and more recently fosphenytoin has been considered a mainstay by the professional community in the treatment of status epilepticus. In recent years, an increasing number of drugs and/or drug combinations have indicated a potential to improve seizure activity on EEG.

Design/Methods: After approval from IRB, a retrospective database was created to review patients diagnosed with status epilepticus along with refractory and super refractory status epilepticus at Tufts Medical Center in Boston MA from 2015-2020. Various clinicopathologic variables and medications were tabulated in such patients who were administered phenytoin or fosphenytoin and a clinical analysis was performed to determine and highlight the efficacy of such treatment.

Results: The treatment of status epilepticus involves complex decision making with regards to the comorbidities and variables associated with the condition. These were tabulated along with the medication decisions made over the course of each status episode. This study indicates that Phenytoin or fosphenytoin terminated seizures as both first line therapy and a later choice in the treatment of status epilepticus.

Conclusions: While the evolving literature indicates that newer antiseizure drugs are available, phenytoin and or fosphenytoin are relatively inexpensive and readily available medications that could still prove to be an integral part of seizure management in the acute setting despite the existence of newer pharmacotherapies.

Background

Status epilepticus is a neurological emergency caused by continuous epileptic activity that can last from minutes to days and timely and effective management of these seizures is essential in the treatment of these patients [1-12]. Phenytoin and more recently fosphenytoin has been considered a mainstay by the professional community in the treatment of status epilepticus and In recent years, an increasing number of newer drugs and/or drug combinations have been noted to have the potential to treat seizures and or status epilepticus [1-12]. This study seeks to characterize how phenytoin and fosphenytoin may prove to be an integral part of seizure management in the acute setting either as first line or other sequential adjunctive therapy despite the existence of other medications and newer pharmacotherapies.

Design/Methods

After approval from IRB, a retrospective database was created to review patients diagnosed with status epilepticus along with refractory and super refractory status epilepticus at Tufts Medical Center in Boston MA from 2015-2020. Various clinicopathologic variables(demographics such as age, sex, number of medications and order line of treatment with phenytoin or fosphenytoin and dose, days under treatment, presumed etiologies of status epilepticus and a comparison among the phenytoin and fosphenytoin groups) were tabulated in such patients who were administered phenytoin or fosphenytoin and a descriptive clinical analysis was performed to determine and highlight the efficacy of such treatment.

Results

45 patients were identified to be in Status Epilepticus on EEG at Tufts Medical Center in the past 5 years during which phenytoin or fosphenytoin were used while undergoing inpatient video EEG Long term monitoring. Seizure etiology varied within the group. The most common etiologies in this population were SDH (15%), infection (14%), medication non-compliance (8%), cardiac arrest (8%), brain tumor (7%), overdose (7%), and stroke (7%). 15(20%) of these patients had a prior diagnosis of epilepsy. The mean age of patients in this population was 55 years old. There were 19 males and 26 females in this subgroup. The use of phenytoin or fosphenytoin in our series resulted in an approximately 82% rate of termination of SE when used either as 1st or subsequently administer adjunctive therapy. Termination was achieved at similar rates, 81% (21/26), in patients that did not receive phenytoin or fosphenytoin. Among patients that did not receive phenytoin or fosphenytoin, 14 (52%) of these patients eventually passed away in their hospital stay, compared with 12 (26%) in those that did receive phenytoin. The average number of anti-epileptic drugs required to terminate seizures was 3.89, which was similar with the non-Phenytoin or fosphenytoin group at 3.78. There was no difference between the mean average times spent in status between phenytoin and non-phenytoin groups.

The average dose of Phenytoin administered after an appropriate 10-20mg/kg loading dose intravenously in this treatment population was 130mg TID, or 390 mg total daily. Phenytoin was initiated as the first-line treatment in 27 of these patients and was effective at resolving seizures in 22 (81.5%) cases. The remaining 5 (19%) patients passed away after respiratory failure or cardiac arrest. Phenytoin was started alongside levetiracetam and Lorazepam in the majority (>50 %) of these cases. As a second-line or later treatment, phenytoin or fosphenytoin was added in 18 cases and was a part of successful management in 15 (83.3%) patients. In 7 of these cases, seizure termination can be attributed, by electrographic and clinical evidence, to administration of phenytoin or fosphenytoin after multiple drug regimens were previously attempted. 3 (17%) patients in this adjuvant group passed away due to respiratory failure. We found from chart reviews in our study mentioned that phenytoin was discontinued due to side effects, intolerability, or poor clinical response in 17 % of the cases in which it was implemented in our series (Tables 1-6).

Table 1: Patients in whom phenytoin or fosphenytoin was used 1st line.

Age of status	Sex	Load Drug	Load	Avg Dose	Max Dose	Min Dose	Starting Dose	Time in Status	Days Used	Outcome	# of AEDs	When Started
72	M	Phenytoin	1g	100mg TID	100mg TID	100mg TID	100mg TID		6	Passed	4	1
72	F	Phenytoin	1g	100mg TID	100mg TID	100mg TID	100mg TID		17	Passed	4	1
52	M	Phenytoin	20mg/kg.600	116mg TID	150mg TID	100mg TID	100mg TID		8	Passed	4	1
82	M			200mg TID	200mg TID	200mg TID	200mg TID	10	3	Resolved	5	1
40	M	Phenytoin	1.5g	250mg TID	250mg TID	250mg TID	250mg TID	3	1	Resolved	5	1
34	M	Phenytoin	load, 1g	135mg TID	150mg TID	100mg TID	100mg TID	11	10	Resolved	6	1

72	F		20mg/ kg.600	100mg TID	100mg TID	100mg TID	100mg TID		3	Resolved	2	1
28	M		500mg, 500mg	116mg TID	150mg TID	100mg TID	100mg TID		6	Passed	5	1
58	F		1800mg, 400mg	100mg TID	100mg TID	100mg TID	100mg TID	3	5	Resolved	3	1
67	F		150mg					3	1	Resolved	3	1
68	F		20mg/ kg.600	100mg TID	100mg TID	100mg TID	100mg TID	6	1	Resolved	3	1
58	F		1.5g, 1g	250mg TID	100mg TID	100mg TID	100mg TID	7	9	Resolved	4	1
22	F		20mg/kg	100mgTID	100mg TID	100mg TID	100mg TID	1	1	Resolved	3	1
58	F	Fosphe-nytoin	1.5g, 500mg	162.5mg TID	100mg TID	100mg TID	100mg TID	2	4	Resolved	3	1
76	F		20mg/kg	100 mgTID	100mg TID	100mg TID	100mg TID	3	4	Resolved	4	1
24	F			100 mgTID	100mg TID	100mg TID	100mg TID	2	3	Resolved	3	1
70	F		1.5g					7	1	Resolved	4	1
28	F		load	100 mgTID	100mg TID	100mg TID	100mg TID	1	1	Resolved	3	1
41	F		200mg	140mg TID	150mg TID	100mg TID	100mg TID	27	23	Resolved	7	1
36	M		200mg/kg	100 mgTID	100mg TID	100mg TID	100mg TID	1	2	Resolved	4	1
45	M		900mg					1	1	Resolved	4	1
91	F			100 mgTID	100 mg-TID	100mg TID	100mg TID		3	Passed	5	1
61	M		load	112.5mg TID	125mg TID	100mg TID	100mg TID	3	6	Resolved	3	1
54	F		300mg, 300mg	142mg TID	200mg TID	100mg TID	100mg TID	3	7	Resolved	5	1
41	M		1g, 500mgx5 load	141mg TID	150mg TID	100mg TID	100mg TID	16	17	Resolved	6	1
28	M		load	100mg TID	100mg TID	100mg TID	100mg TID	1	2	Resolved	1	1
62	F		450mg x 2 load	100mg TID	100mg TID	100mg TID	100mg TID	2	3	Resolved	4	1
							Avg Time in Status	5.380952381		Passed		
							w/o outliers	40421052632		Resolved		

Table 2: Patients in whom phenytoin/fosphenytoin was started as NOT a first line agent Note Time in status is reported in days.

Age of status	Sex	Avg Dose	Max Dose	Min Dose	Starting Dose	Time in Status	Days Used	Status Duration	Outcome	# of AEDs	When Started	# of AED Used
57	M	300mg TID	300mg TID	300mg TID	300mg TID	2	1	1	Resolved	6	Last	5
76	F	100mg TID	100mg TID	100mg TID	100mg TID	3	2	1	Resolved	4	Last	4
19	M	100mg TID	100mg TID	100mg TID	100mg TID	5	5	1	Resolved	4	Last	4
57	M	100mg TID	100mg TID	100mg TID	100mg TID		11		Passed	4	Second	2

52	F	100mg TID	100mg TID	100mg TID	100mg TID	6	4	3	Resolved	3	Last	3
73	F	134mg TID	150mg TID	100mg TID	100mg TID	23	26	19	Resolved	3	Last	3
70	F	100mg TID	100mg TID	100mg TID	100mg TID	6	5	5	Resolved	4	Second	2
50	M	133mg TID	150mg TID	100mg TID	100mg TID	1	3	1	Resolved	3	Second	2
31	M	100mg TID	100mg TID	100mg TID	100mg TID	9	5	5	Resolved	4	Second	2
75	F					1	1	1	Resolved	5	Second	2
69	F	112.5mg TID	125mg TID	100mg TID	100mg TID	3	3	2	Resolved	3	Second	2
63	M	100mg TID	100mg TID	100mg TID	100mg TID	9	8	8	Resolved	4	Second	2
57	M	100mg TID	100mg TID	100mg TID	100mg TID	2	1	1	Resolved	5	Second	2
53	F	100mg TID	100mg TID	100mg TID	100mg TID		3		Passed	2	Last	2
59	F	100mg TID	100mg TID	100mg TID	100mg TID		3		Passed	2	Second	2
64	F	116mg TID	150mg TID	100mg TID	100mg TID	2	6	2	Resolved	4	Second	2
73	M	94mg TID	100mg TID	75mg TID	100mg TID	3	4	2	Resolved	4	Second	2
63	F	130mg TID	130mg TID	130mg TID	130mg TID	3	3	1	Resolved	3	Last	3
					Avg Time in Status	5.2			Passed			
					w/o outliers	4			Resolved			

Table 3: Etiologies of Status Epilepticus at Tufts Medical Center.

Causes	No. (n=73)
Unknown/Multifactorial	15
Infection	11
SDH/ICH	10
Cardiac Arrest/PEA	7
Med Non-compliance	6
Tumor	5
Overdose	5
Stroke	5
Heart Failure	2
HSV Encephalopathy	1
Cavernous Malformation	1
TBI	1
Med Change	1
Shunt Placement	1

Burr Hole Placement	1
Asthma status	1

Table 4: Comparison of clinical outcomes between treatment with phenytoin and without phenytoin.

	With Phenytoin (n=45)	Without Phenytoin (n=26)
Seizure termination	37 (82.2%)	21 (80.7%)
Mortality	12 (26%)	14 (52%)
No. of AEDs Required	3.89	3.79

Table 5: Comparison of clinical outcomes between phenytoin first-line versus second-line (or later).

	First-line (n=27)	Second-line (n=18)
Seizure Termination	22 (81.5%)	15 (83%)
Mortality	5 (18.5%)	3 (16.6%)

Table 6: Comparison in number of AEDs used for seizure termination.

	< 3 AEDs (n=16)	3 AEDs (n=15)	> 3 AEDs (n=16)
Seizure Termination	13 (81%)	11 (73%)	12 (86%)

Discussion

Status epilepticus(SE) and Refractory Status Epilepticus (RSE) represent neurological emergencies caused by continuous epileptic activity clinically and electrographically on EEG and recent studies have estimated an incidence between 1.29-73.7/100,000 [1]. Effective management of SE or RSE is essential as early termination of seizures is associated with potentially fewer adverse effects-including neurologic injury, cardiac and respiratory complications, and ICU care [1-6]. Current protocols from the standard of care literature recommend initial treatment with benzodiazepines, followed by one of numerous anti-epileptic drugs and evolving literature includes multiple anti-seizure medications such as phenytoin, levetiracetam, valproic acid, and lacosamide, among others, and they have all been shown to have some efficacy in treating SE [1-7]. There is little high-quality evidence available, however, to guide clinicians in their specific selection or ordering of such adjunctive therapies when indicated of these modifications. Phenytoin used since the early 1900's has been considered a standard drug within the professional community in the treatment of status epilepticus as clinicians are generally experienced in its use and the literature indicates that phenytoin or the newer pro-drug fosphenytoin which is biologically produced as phenytoin once administered are therefore commonly used and may be readily available at most hospitals, and accepted as effective in treating seizures. The mechanism of action within the brain and its systemic effects are well-studied or are also the subject of study although there have been an increasing number of available medications thought to exhibit fewer or potentially less severe side effects as compared to phenytoin or fosphenytoin [8-12].

The challenge for optimal management is choosing which drugs (or combinations of drugs) will most effectively assist in the management of status epilepticus. In our series of a broad category of treating SE, it was noted that phenytoin or fosphenytoin treated SE and RSE as either first line or subsequently adjunctively in certain cases [8-12]. Limitations of the current study include that this study involves only a small number of cases under study, there was potentially significant heterogeneity in the clinical variables and real-time decision making was done without a specific protocolled treatment plan as in a forward prospective randomized clinical trail. Additionally the current case series includes various cases with either unknown durations of status epilepticus or had a heterogenous timing or timeline of therapy which may be impacting clinical outcome, it may be stated that there may have been somewhat arbitrary implementation of phenytoin or phosphenytoin as opposed to other medications without further rationale or indication specified from chart review retrospectively, Furthermore, the lack of standardization for continuing such therapy for a certain duration among dosing regimens remain without guidelines and is overall not studied, and follow up was limited to status epilepticus being treated in a solitary admission on a case by case basis which timelines and comorbid clinical courses, concomitant medications and comorbidities varied potentially significantly from case to case.

Additionally, lack of analyses of the cases involving other combination therapies exhaustively in comparison which either had resolution with another medication or combination or did not have successful treatment of status epilepticus compared to the current dataset that were treated as noted remain additional

limitations or undefined elements in the current study although such was attempted as noted above. Cases involving ictal continuum at any point were excluded [11]. Although there was agreement retrospectively among the among the interpreters retrospectively in this analysis of the EEG dataset, verification with multiple readers was not performed in real time during a protocolled approach to treatment although ACNS criteria for identification of electrographic seizures and EEG terminology was used [11]. This study does not analyze whether clinically apparent seizures versus electrographic seizures yielded different decision making or outcome or pharmacotherapy or other clinical parameters of significance. No study of long term clinical outcome beyond termination or not of seizure activity or death during such admission as indicated was made with this dataset. Nonetheless, despite the noted confounding issues- the limited data derived from this study indicates that phenytoin or fosphenytoin may effectively terminate SE and RSE within multi-drug regimens for the management of SE and RSE despite the availability of concomitant other available and newer therapies [1-13].

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