RESEARCH PAPER

Efficacy, Tolerability and Serum Phenytoin Levels after Intravenous Fosphenytoin Loading Dose in Children with Status Epilepticus

KAVITA SRIVASTAVA, SHIRISH BHARTIYA, VRUSHABH GAVLI, RAHUL PATIL AND SUREKHA RAJADHYAKSHA

From Pediatric Neurology Unit, Department of Pediatrics, Bharati Vidyapeeth Deemed University Medical College, Pune, India. Correspondence to: Dr Kavita Srivastava, Professor in Pediatrics, 3rd floor, Bharati Hospital, Katraj, Pune 411 043, India. kavisri1970@gmail.com

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Objective: To evaluate the efficacy and tolerability of intravenous fosphenytoin in children with status epilepticus, and resulting serum total phenytoin levels.

Methods: In this prospective study, 51 children aged less than 18 years received intravenous loading dose of fosphenytoin (18-20 mg/kg). Serum total phenytoin levels were estimated at 90 -100 minutes. Outcomes studied were (*i*) seizure control and local and/ or systemic adverse effects in next 24 hours and (*ii*) phenytoin levels and its correlation with dose received, seizure control and adverse effects.

Results: The actual dose of fosphenytoin received varied from 15.1 to 25 mg/kg. Seizures were controlled in 45 (88%) children and, two required additional dose of 10 mg/kg. None of the children showed any local or systemic adverse effects. Serum total phenytoin levels were in the therapeutic range (10-20 µg/mL) in 12 (23.5%), sub-therapeutic in 16 (31.3%) and supra-therapeutic in 25 (49%) children. There was weak correlation of the phenytoin levels with dose of fosphenytoin received, seizure control, or adverse effects.

Conclusion*:* Intravenous fosphenytoin loading dose of 20 mg/kg is effective in controlling seizures in 88% of children with status epilepticus, with a good safety profile. Seizure control and adverse effects appear to be independent of serum total phenytoin levels achieved.

Keywords: *Anticonvulsant, Management, Seizure control, Therapeutic levels.*

Intravenous Phenytoin (PHT) is the first long-acting drug (after benzodiazepines) recommended for the treatment of status epilepticus [1,2]. Fosphenytoin (FOS) is a pro-drug which is rapidly converted to PHT and preferred due to less incidence of thrombophlebitis and cardiotoxicity [3,4]. PHT follows non-linear kinetics, causing unpredictable blood levels, with higher levels associated with cardiac arrhythmias and hypotension. PHT concentrations may be influenced by ethnicity due to its hepatic metabolism through cytochrome P450 enzymes [5,6].

While it is recommended to maintain serum total PHT levels in the therapeutic range of 10 to 20 µg/mL, monitoring is not done routinely in India, possibly due to cost or feasibility issues. Efficacy and safety of FOS have been stressed by few authors, and others have evaluated the pharmacokinetics in status epilepticus [7-11]. Hence this study was done to evaluate the efficacy and tolerability of loading dose of 20 mg/kg of intravenous FOS in children admitted for status epilepticus and to, correlate the serum PHT levels after 90-100 minutes of loading with actual dose received, seizure control and adverse effects.

METHODS

This was an observational study conducted in emergency ward and pediatric intensive care unit (PICU) of a medical college affiliated hospital over 10 months (December, 2016 to September, 2017). Institutional Ethics Committee approval was taken, and written informed consent from parents was obtained to participate in the study.

Accompanying Editorial: Pages 209-210.

Children aged one month to 18 years with status epilepticus were enrolled in the study. Status epilepticus was defined as seizure duration of more than 30 minutes or two or more seizures without regaining consciousness. Those who were already on oral PHT or loaded with any other antiepileptic drug outside the hospital were excluded.

All patients received a standard protocol for securing airway, oxygenation, and circulation. IV Lorazepam 0.1 mg/kg followed by IV FOS [(Brand Fosolin, Zydus Cadilla), content: 50 mg/mL of phenytoin equivalents (PE)] at a dose of 20 mg/kg for estimated weight (or actual weight, if known) was administered.

Blood sample (5 mL) was obtained at 90 to 100 minutes (after loading dose) to determine the serum total PHT levels, serum albumin, and creatinine. The PHT levels were estimated using CLIA (Chemiluminescence immunoassay) method by Immulite 1000 machine (Siemens, Los Angeles CA 90045 USA. If there was a breakthrough seizure, a second dose of 10 mg/kg of IV FOS was administered.

A detailed history of perinatal events, development, family history, and etiology of seizures were recorded, along with physical and neurological examination. Seizure control was defined as cessation of any clinical seizure activity. The total duration of seizure, need of additional dose/ other anti-epileptic drugs, and any adverse effects were recorded for the next 24 hours. The patients were followed till discharge/death, and final outcome noted.

Accurate weight was obtained after recovery and the actual dose received in mg/Kg was recalculated. Optimal dose was defined as 18-20 mg/kg of PE, subnormal if less than 18 mg/kg and supra-normal if more than 20 mg/kg. PHT levels were considered to be in the therapeutic range between 10-20 µg/mL, below 10 µg/mL as sub-therapeutic, above 20 µg/mL as supra-therapeutic and more than 40 µg/mL to be in toxic range. The outcome studied for efficacy was the number of patients with clinical control of seizures in next 24 hours. For tolerability, number of patients with local (cording of vein, erythema, and swelling at IV site) and systemic adverse effects (*e.g.* vomiting, nystagmus, ataxia etc.) was recorded.

Statistical analysis: Linear regression of serum PHT levels with actual loading dose received was plotted, and Pearson correlation coefficient was computed. PHT levels were further analyzed to see whether they correlated with seizure control and adverse effects.

RESULTS

Fifty-one children (54.9% males) were prospectively enrolled. Age distribution was as follows: below one year (*n*=9), 1-5 years (*n*=19), 5-10 years (*n*=14) and more than ten years (*n*=9). The seizure types were generalized tonic-clonic seizure (*n*=40), focal seizure with impaired awareness (*n*=8), or evolving into bilateral convulsive seizure (*n*=3). Among the fifteen children who were already diagnosed with epilepsy, 11 were on antiepileptic medications: valproate (*n*=2), topiramate (*n*=2), oxcarbazepine (*n*=2), levetiracetam (*n*=2) and nitrazepam (*n*=2). One child was on both valproate and levetiracetam. Etiologies were febrile status epilepticus (*n*=10), prior brain insult (*n*=7) meningitis (*n*=6), traumatic brain injury (*n*=4), sepsis (*n*=2), subdural hematoma (*n*=1), neurocysticercosis (*n*=1), metabolic disorder (*n*=1) and unknown (*n*=19).

Among the 51 children, 32 (62.7%) received optimal dose of 18-20 mg/kg, 16 (31.3%) received supra-normal, and rest three received sub-normal doses. The dose varied from 15.1 to 25 mg/kg (mean dose 20.22 mg/kg) Serum albumin and creatinine were within normal range in all children.

Forty-five out of 51 (88%) patients achieved seizure control after the first dose. All children with febrile status epilepticus (*n*=10) were controlled after a single dose. Two patients (with unknown etiology) had breakthrough seizures (after 3 and 12 hours of loading dose), which were subsequently controlled after second dose of 10 mg/kg. Thus overall, 47 (92%) children achieved seizure control on FOS alone.

None of the children showed any local or systemic adverse effects, even with PHT levels in the supratherapeutic or toxic range. Two patients with meningitis showed local cording of vein, attributed to vancomycin.

Table I Serum Total Phenytoin Levels and Seizure Control in Children and Loading Dose of Fosphenytoin (*N*=51)

Dose received	*Sub- normal dose (n=3)*					*Optimal dose (n=32)*					*Supra-normal dose (n=16)*				
Phenytoin levels (µg/mL)	*Very low <2.5*	*Low 2.5 to 10*	*In range 10-20*	*High 20-40*	*Toxic >40*	*Very low <2.5*	*Low 2.5 to 10*	*In range 10-20*	*High 20-40*	*Toxic >40*	*Very low <2.5*	*Low 2.5 to 10*	*In range 10-20*	*High 20-40*	*Toxic >40*
Patients, *n*	1	-	1	1	-	8	3	7	11	3	3	1	4	7	1
*Seizure control achieve*d															
Yes	1	-	1	1	-	8	3	6	10	1	2	1	3	7	1
No	0	-	0	0	-	0	0	1*	1*	2#	1*	0	1	0	0

*Sub-normal dose: <18 mg/kg; Optimal dose: 18-20 mg/kg; Supra-normal dose: >20 mg/kg; *Needed second dose; #Needed continuous midazolam infusion.*

WHAT IS ALREADY KNOWN?

- Fosphenytoin shows good efficacy in control of seizures, with less risk of adverse effects.

WHAT THIS STUDY ADDS?

- Fosphenytoin showed good efficacy in children with status epilepticus, with good safety profile.
- Serum total phenytoin levels at 90-100 minutes showed poor correlation with the dose of fosphenytoin received.

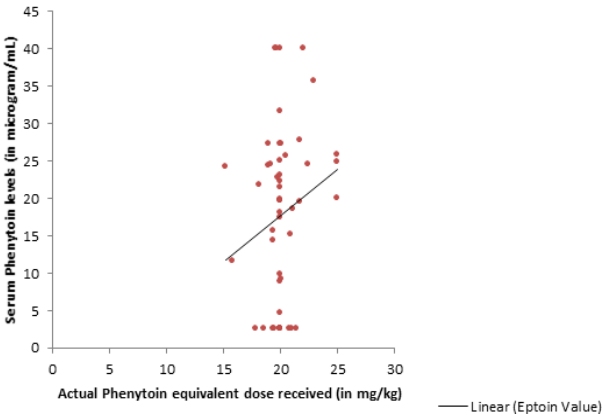

Fig. 1 *Correlation of serum phenytoin levels with the actual dose of intravevous fosphenytoin received (R^2=0.038).*

We found a weak correlation between the dose of intravenous FOS received and the serum PHT levels, as depicted in ***Fig*.1**. Serum PHT levels were in therapeutic range in 12 (23.5%), supra-therapeutic in 23 (45%) and sub-therapeutic in 16 (31.3%) children, as shown in ***Table* I**. Seizure control after first dose was achieved in 15 out of 16 (93.7%) children with sub-therapeutic levels, 10 out of 12 (83.3%) with therapeutic and 20 out of 23 (86.9%) with supra-therapeutic levels. One child each in sub-therapeutic and therapeutic levels required second dose after 3 and 12 hours, respectively.

DISCUSSION

The present study revealed good efficacy of IV FOS (with a dose of 18-20 mg/kg) in controlling status epilepticus in children, similar to findings of other studies [7,8,10,11]. However, in an African study, seizures were controlled in only 36% and 44% patients who received PHT and FOS, respectively each in the dose of 18 mg/kg [9].

In our study, intravenous FOS demonstrated an excellent safety profile, even among those with PHT levels in supratherapeutic or toxic range in 23 (45%) patients. As compared to PHT, IV FOS has lesser rates of venous irritation, mechanical ventilation and use of inotropic agents [11-13]. However, in adults, 29 cardiac events, including ten deaths were reported between 1997 to 2003, although many of these patients had pre-existing cardiac pathology [14].

In our study, only 35 patients (68.62%) achieved PHT levels in therapeutic or supratherapeutic range. Single-dose is shown to achieve and maintain therapeutic levels up to 24 hours after loading dose, irrespective of body mass index [8,15-17]. One study suggested 22.5 mg/kg may be a better dose to achieve therapeutic levels in children [18]. Ogutu, *et al*. [9] showed comparable serum levels when intravenous FOS and PHT were given (dose 18 mg/kg) and FOS achieved peak levels faster (mean 0.08 hours) as compared to 0.37 hours for PHT.

We found a weak correlation between the FOS dose and PHT levels achieved. Selioutski, *et al*. [19] also found similar results, 63% of those receiving 15-20 mg/kg dose and 51% of those receiving 20-55 mg/kg dose did not achieve levels of 20 µg/mL or more within the first 6 hours; while some patients achieved levels of >20 µg/mL despite receiving low doses.

Therapeutic drug monitoring of PHT levels is considered necessary to ensure non-toxic levels, and should preferably be done at least one hour after loading [6]. In our study, seizure control did not depend on serum PHT levels. Also, a low incidence of adverse effects even with blood levels in toxic range is reassuring. Thus, we did not find any additional benefit of monitoring PHT levels, though numbers are small. Seizure control (without adverse effects) may be a better measure of clinical efficacy as compared to blood levels, which indicate pharmacokinetic efficacy.

Due to limited funding, our sample size was small, and PHT levels could not be repeated at later time intervals to ascertain whether they remain in the therapeutic range. We did not exclude patients who were already on other anti-epileptic drugs before admission, which can influence PHT levels.

In future studies, serum PHT levels can be serially measured at different time/points after the loading dose. Efficacy, tolerability, and pharmacokinetics of

intramuscular loading dose of FOS should also be studied, along with a detailed pharmaco-economic assessment.

A single loading dose of intravenous FOS (18-20 mg/kg) is effective in controlling status epilepticus in 88% of children with very low risk of adverse events. It should be preferred over PHT as second-line drug for status epilepticus. Serum PHT levels were in therapeutic and supratherapeutic range in only 68.6% at 90-100 minutes of loading, and appear to be independent of dose received.

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