

Fosphenytoin in Status Epilepticus: The Ice Needs to be Broken

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Status epilepticus (SE) is the most common neurological emergency encountered by pediatricians and the incidence is significantly higher in children compared to adults. North London Status Epilepticus in Childhood Surveillance Studies (NLSTEPSS), amongst the largest prospective population-based studies of convulsive SE in children, reported an annual incidence of 18-20 convulsive SE episodes per 100000 population as opposed to 4-6 per 100000 in the adult population [1].

Most pediatric SE guidelines recommend intravenous phenytoin (PHT) as the antiepileptic of choice after benzodiazepines [2,3]. However, various adverse effects have been reported with parenteral PHT, which include fluid incompatibilities, patient discomfort, patient irritation, tissue damage, muscle necrosis and cardiac toxicity [4]. The local adverse effects are related to the poor water solubility of phenytoin. This has led to the emergence of fosphenytoin (fPHT), a phosphate ester of PHT, to obviate the local complications of PHT [5]. fPHT was first approved in USA in 1996 and subsequently in Japan in 2011, and then other countries followed suit [6].

Fosphenytoin is a water soluble prodrug of phenytoin, which rapidly and entirely converts to PHT. Increased solubility of fPHT allows rapid infusion in status epilepticus, which compensates for the delay in the conversion of the prodrug to active metabolite. The mechanism of action and drug interactions are similar to PHT. Till date, no interaction has been reported in terms of the conversion of fPHT to PHT. The recommended loading dose for fPHT is 18-20 mg/kg of phenytoin equivalent at an infusion rate of 100-150 mg/minute [6].

The largest randomized trial evaluating fPHT in status epilepticus, the ESETT trial [7], compared the efficacy of levetiracetam, fPHT and valproate in 384 patients, of which around 40% were children and adolescents. There was no significant difference in terms of seizure control, regaining consciousness at 60 minutes, and frequency of adverse effects. In an Indian pediatric study [8], intravenous fPHT was compared with levetiracetam in

status epilepticus. Time to stop seizure was significantly lesser in the fPHT group. However, seizure control, seizure recurrence, seizure-free duration and intensive care unit and hospital stay were similar in both the groups [8]. In a pediatric study [9] comparing intravenous fPHT with midazolam infusion as a second line agent in febrile status, efficacy of both was found to be similar and the latter was found to be relatively safe. The proportion of patients requiring barbiturate coma, mechanical ventilation and inotropic support and having incomplete recovery from consciousness was also not significantly different between the groups [9].

In the current issue of *Indian Pediatrics*, Srivastava, *et al.* [10] found that of the 51 children who presented with convulsive SE, 92% got controlled with fPHT, reinforcing the fact that it is a highly efficacious drug in convulsive SE, particularly in children. The study by Senthikumar, *et al.* [8] showed control in 84% which could be explained by the fact that it was conducted on a pure pediatric population. In ESETT trial [7] only 45% showed initial control, which may be because this was predominantly in an adult population with a different etiological spectrum. Srivastava, *et al.* [10] reported a weak correlation of serum PHT levels with the original dose of fPHT received, and poor association with control of seizures; however, the serum PHT levels were estimated at 90-100 minutes post fPHT loading dose [10]. These findings could be explained by the fact that PHT follows nonlinear kinetics and early estimation of serum PHT levels may reveal a different picture, when it is following first order kinetics. The maximum serum PHT levels after fPHT administration are achieved at 10-20 minutes [6]. None of the children in the current study showed any adverse effects, highlighting the safety of fPHT in pediatric age group. Although, the chances of local complications are less with fPHT compared to PHT, the incidence of cardiac systemic complications like hypotension and arrhythmia are similar to PHT [6]. Under ideal circumstances, electrocardiogram, blood pressure and respiration should be monitored during fPHT administration. The most notable local complication of

fPHT is purple glove syndrome, which is seen to the tune of up to 45%. This rate is higher with PHT [6].

The existing literature reinforces the fact that fPHT is a safe drug with reasonable efficacy for convulsive SE. However, except for decreased chances of local complications, it does not provide any obvious superiority to PHT. Studies like the present one will go a long way in breaking the ice for fPHT. More studies, including head-to-head comparative trials with PHT, should be planned, particularly in the pediatric population, to establish safety and efficacy.

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