Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus

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Abstract:

AIMS: Status epilepticus is common in children with severe falciparum malaria and is associated with poor outcome. Phenytoin is often used to control status epilepticus, but its water-soluble prodrug, fosphenytoin, may be more useful as it is easier to administer. We studied the pharmacokinetics and clinical effects of phenytoin and fosphenytoin sodium in children with severe falciparum malaria and status epilepticus. METHODS: Children received intravenous (i.v.) phenytoin as a 18 mg kg-1 loading dose infused over 20 min followed by a 2.5 mg x kg(-1) 12 hourly maintenance dose infused over 5 min (n = 11), or i.v. fosphenytoin, administered at a rate of 50 mg x min(-1) phenytoin sodium equivalents (PE; n = 16), or intramuscular (i.m.) fosphenytoin as a 18 mg x kg(-1) loading dose followed by 2.5 mg x kg(-1) 12 hourly of PE (n = 11). Concentrations of phenytoin in plasma and cerebrospinal fluid (CSF), frequency of seizures, cardiovascular effects (respiratory rate, blood pressure, trancutaneous oxygen tension and level of consciousness) and middle cerebral artery (MCA) blood flow velocity were monitored. RESULTS: After all routes of administration, a plasma unbound phenytoin concentration of more than 1 microg x ml(-1) was rapidly (within 5-20 min) attained. Mean (95% confidence interval) steady state free phenytoin concentrations were 2.1 (1.7, 2.4; i.v. phenytoin, n = 6), 1.5 (0.96, 2.1; i.v. fosphenytoin, n = 11) and 1.4 (0.5, 2.4; i.m. fosphenytoin, n = 6), and were not statistically different for the three routes of administration. Median times (range) to peak plasma phenytoin concentrations following the loading dose were 0.08 (0.08-0.17), 0.37 (0.33-0.67) and 0.38 (0.17-2.0) h for i.v. fosphenytoin, i.v. phenytoin and i.m. fosphenytoin, respectively. CSF: plasma phenytoin concentration ratio ranged from 0.12 to 0.53 (median = 0.28, n = 16). Status epilepticus was controlled in only 36% (4/11) following i.v. phenytoin, 44% (7/16), following i.v. fosphenytoin and 64% (7/11) following i.m. fosphenytoin administration, respectively. Cardiovascular parameters and MCA blood flow were not affected by phenytoin administration. CONCLUSIONS: Phenytoin and fosphenytoin administration at the currently recommended doses achieve plasma unbound phenytoin concentrations within the therapeutic range with few cardiovascular effects. Administration of fosphenytoin i.v. or i.m. offers a practical and convenient alternative to i.v. phenytoin. However, the inadequate control of status epilepticus despite rapid achievement of therapeutic unbound phenytoin concentrations warrants further investigation