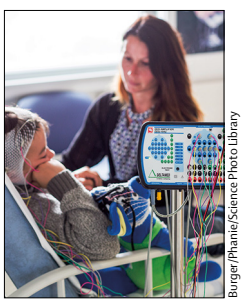
Levetiracetam no better than phenytoin in children with convulsive status epilepticus



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Although frightening to watch, most generalised convulsive seizures in both adults and children stop within about 2 min with or without treatment. Seizures that last more than 5 min, however, usually do not stop without anticonvulsant treatment. Initial treatment for these patients in status epilepticus is rapidly and adequately dosed administration of a benzodiazepine. Guidelines for benzodiazepine dosing are based on high-quality data from randomised controlled trials.[1–3] Status epilepticus, treated according to guidelines, can be expected to resolve in about 70% of patients after first-line treatment with benzodiazepines.[3] In those 30% of patients with seizures that do not respond to first-line treatment with benzodiazepines, guidelines recommend treatment with any of several second-line anticonvulsants.[4,5] Unfortunately, guidelines for second-line anticonvulsants in patients with status epilepticus have had to rely on scant and relatively low-quality data from observational studies or very limited trials. Few data from large randomised trials have been available to determine which agents are most effective, or even if any of the recommended second-line anticonvulsants work in this setting. That is, until now. In *The Lancet*, Stuart Dalziel and colleagues[6] and Mark Lyttle and colleagues[7] report two separate clinical trials comparing treatment with phenytoin versus levetiracetam in children with convulsive status epilepticus that persisted after benzodiazepine treatment.

Both the Convulsive Status Epilepticus Paediatric Trial (ConSEPT),[6] done in Australia and New Zealand, and the Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus in children (EcLiPSE) trial,[7] done in the UK, were designed to determine whether levetiracetam was superior to phenytoin in children with status epilepticus. Children were eligible to be enrolled if 3 months to 16 years of age in the ConSEPT, and if 6 months to 18 years in EcLiPSE. Similar numbers of girls and boys were enrolled in both trials. The primary outcome measures in the two trials were the proportion of children with clinical cessation of seizure 5 min after completion of infusion of the study drug (ConSEPT) and the time from randomisation to seizure cessation (EcLiPSE). Levetiracetam was neither more effective nor safer than phenytoin in either trial. In ConSEPT, seizure cessation occurred in 68 (60%) of 114 children randomly assigned to phenytoin and 60 (50%) of 119 children randomly assigned to levetiracetam at a median of 22 min (IQR 9–49) and 17 min (5–30) after the start of study drug infusion. In EcLiPSE, seizure cessation after a single dose of second-line treatment occurred in a similar proportion of children in each group (see table 3 of Article) and at similar median times (see appendix of Article) after the start of study drug infusion.

The consistency of the findings in these contemporaneous, but independent trials is notable. We serve in the leadership of a third trial (ESETT, NCT01960075, done in the USA), which is also comparing levetiracetam and phenytoin, as well as valproate, in children and adults with continued generalised convulsive status epilepticus after benzodiazepines, the results of which are forthcoming.[8,9] We look forward to exploring how our data complement the findings from ConSEPT and EcLiPSE.

The strengths of both trials are their clinical relevance. Despite the challenges of conducting high-quality clinical trials in the fast-paced, sometimes chaotic, emergency settings, ConSEPT and EcLiPSE effectively integrated the research into the routine clinical resuscitation workflow of these acutely ill patients, making the results relevant and credible. From these trials, we can be confident that slightly more than half of children with convulsive status epilepticus will clinically resolve after treatment with either of these second-line anticonvulsants. Whether a 50% clinical response rate is strong or weak remains a controversy, but certainly allows for improvement.

The opportunity to improve emergency treatment of children with convulsive status epilepticus might derive from weaknesses inherent in both of these trials and the clinical care they reflect. In both trials, the intervention was delivered without masking, and the primary outcome was determined clinically by the treating physicians. However, deciding exactly when a child's seizures have stopped can be subjective. Before

stopping, convulsion can stutter or pitter out rather than cease abruptly. Video recording and masked reassessment of the outcomes in ConSEPT was used as an innovative quality assessment tool to mitigate this weakness. This process and ultimately a result different from that for which the investigators had hoped in both trials suggest that this potential source of bias did not drive the findings of the trials. The subjectivity of the clinical outcome, however, persists. On the one hand, clinical response to therapy is the only patient-oriented outcome that matters. On the other hand, clinical response to therapy is a black box. The relevant contributions of several factors cannot be directly observed or known in these studies. Subjectivity not only complicates clinical determination of cessation of seizures but also complicates subsequent clinical decision making about when to use additional rescue doses of anticonvulsants and when to proceed to endotracheal intubation.[10] Similar clinical outcomes with both drugs in these trials might indicate a similar pharmacological effect on seizures but alternatively might show that clinical factors other than the drugs might be driving the clinical outcome more strongly. If so, research to improve clinical outcomes might have to assess more than just the choice of medication.

As we move forward, discovery will require innovations that attempt to disentangle the effects of pharmacology, electrophysiology, and clinical decision making on clinical response. For example, we will need new technology to practicably acquire and interpret electroencephalography in the earliest phases of emergency care in both practice and research. Clinical trials can also expand the use of video monitoring or develop other innovations to better understand practice variability with regard to whether patients undergo endotracheal intubation during or after seizures.

There are good reasons to believe that how we treat children (and adults) with convulsive status epilepticus in the first minutes and hours after ictus is critically important. ConSEPT and EcLiPSE are one step towards learning how best to care for these patients.

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