Levetiracetam as an alternative to phenytoin for second-line emergency treatment of children with convulsive status epilepticus: the EcLiPSE RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The EcLiPSE RCT

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Scientific summary

Background

Convulsive status epilepticus is the most common life-threatening neurological emergency in childhood, with a mortality rate of 1–5%. These children are also at risk of significant morbidity, with acute and chronic impacts on the family and health and social care systems. Intravenous phenytoin (Epanutin, Pfizer Inc., New York, NY, USA) [fosphenytoin (Pro-Epanutin, Pfizer Inc.) in the USA] is the current recommended first-choice second-line treatment in children aged ≥ 6 months. However, there is no good randomised controlled trial evidence for its use and it is associated with significant and potentially serious side effects. Emerging evidence suggests that intravenous levetiracetam (Keppra, UCB Pharma, Brussels, Belgium) may be clinically effective as a second-line agent for convulsive status epilepticus, with fewer reported adverse effects. This trial aimed to determine whether intravenous phenytoin or intravenous levetiracetam is more effective and safer in treating childhood convulsive status epilepticus.

Aims and objectives

The study objectives were to determine:

1. whether intravenous phenytoin or intravenous levetiracetam is the more efficacious second-line anticonvulsant for the emergency management of convulsive status epilepticus in children
2. whether or not intravenous levetiracetam is associated with fewer adverse reactions or events than intravenous phenytoin
3. the potential barriers and solutions to recruitment and consent in the EcLiPSE trial to inform future trials with regard to recruiter training and trial conduct in this clinical setting (i.e. a nested consent study).

Methods

Study design

This was a Phase IV, multicentre, parallel-group, randomised controlled, open-label superiority trial that took place in a paediatric emergency department. Following first-line treatment for convulsive status epilepticus, children with a continuing convulsive seizure were randomised to receive either phenytoin (20 mg/kg, with a maximum of 2 g) or levetiracetam (40 mg/kg, with a maximum of 2.5 g) intravenously. The primary outcome was time from randomisation to cessation of all visible signs of convulsive status epilepticus. All 'visible signs of convulsive activity' was defined by cessation of all continuous rhythmic motor activity, as determined by the treating clinician. Secondary outcome measures were the need for further anticonvulsants to manage the convulsive status epilepticus, rapid sequence induction for ongoing convulsive status epilepticus, admission to critical care (either a high-dependency unit or a paediatric intensive care unit) and serious adverse reactions. Patients were randomised and treated without prior consent, with consent sought after the emergency situation.

The consent study methods included questionnaires and interviews with parents of randomised children, interviews and focus groups with EcLiPSE trial practitioners and audio-recorded trial discussions.

Eligibility criteria

Inclusion criteria

- Males and females aged 6 months to 17 years and 11 months (inclusive).
- The presenting seizure was a generalised tonic–clonic, generalised clonic or focal clonic convulsive seizure that required second-line treatment to terminate the seizure (i.e. convulsive status epilepticus).
- First-line treatment administered in accordance with advanced paediatric life support guidelines or the child's personalised rescue care plan to try to terminate the presenting seizure.

Eligibility notes

Patients with the following features were eligible for inclusion in the trial, assuming that all other inclusion and exclusion criteria were met.

- Patients administered more than two doses of benzodiazepines, which is above the recommended dose in advanced paediatric life support guidelines.
- Patients whose personalised rescue care plan included rectal paraldehyde as the first-line treatment.
- Patients receiving oral phenytoin or levetiracetam as part of their regular maintenance oral antiepileptic drug regime.

Exclusion criteria

- Absence, myoclonic or non-convulsive status epilepticus, or infantile spasms.
- Patients with a known or suspected pregnancy.
- Patients with known contraindication or allergy to levetiracetam or phenytoin. This included when the child's personalised rescue care plan stated that the child never responded to, or had previously experienced a severe adverse reaction to, phenytoin, levetiracetam or both.
- Patients with known renal failure (patients on peritoneal or haemodialysis, or with renal function that is < 50% expected for age).
- Previous administration of a second-line antiepileptic drug prior to arrival in the emergency department.
- Patients known to have previously been treated as part of the EcLiPSE trial.

Parents/legal representatives who did and did not consent to their child's participation in the trial and all practitioners involved in screening, recruiting, randomising and consenting parents/legal representatives were eligible to take part in the consent study.

Recruitment

Patients were assessed by clinical staff to determine if they were eligible for the trial.

No attempt was made to obtain fully informed consent for the trial from the participant/parent/legal representative prior to randomisation or treatment. Consent was ideally sought within 24 hours after randomisation and patient follow-up was completed, regardless of whether or not a second-line treatment was administered. If consent was refused, all data and samples collected for the trial were destroyed.

Consent was sought from parents/legal representatives to participate in each element of the consent study as part of the EcLiPSE trial consent process. E-mail invitations were sent to practitioners, inviting them to participate in a focus group or an interview.

Randomisation

Eligible children were randomised following completion of first-line therapy if the convulsive status epilepticus continued. This enabled the preparation and administration of the allocated treatment in a time frame consistent with advanced paediatric life support guidance for the management of convulsive status epilepticus.

If the convulsive status epilepticus terminated prior to administration of the allocated treatment but then restarted before the patient left the emergency department, the patient would then be given the allocated treatment. Randomised participants who did not receive a second-line treatment in the emergency department were not included in the primary or secondary analyses.

Participants were randomised to levetiracetam or phenytoin in a ratio of 1 : 1. The randomisation code list was generated by an independent statistician. Randomisation packs were numbered sequentially, and opaque, tamper-proof envelopes were opened in ascending order. Checks were performed periodically to ensure that the correct number of randomisation packs were present and intact, and that the sequential numbering system was maintained. The envelopes contained the first case report form, which was completed in the emergency department during the convulsive status epilepticus episode. Data collected included time of drug administration, convulsive status epilepticus cessation, additional therapy required, adverse events and whether or not the child was discharged from the emergency department or where they were admitted to.

Outcome measures

Primary outcome

The primary outcome was time from randomisation to cessation of all visible signs of convulsive status epilepticus activity, defined as cessation of all rhythmic convulsive activity.

Secondary outcomes

The secondary outcomes were as follows.

1. Need for further anticonvulsants to manage seizures after randomised treatment.
2. Need for rapid sequence induction because of ongoing convulsive status epilepticus.
3. Need for admission to a critical care unit (i.e. high-dependency unit or paediatric intensive care unit).
4. Serious adverse reactions, which included death, Stevens–Johnson syndrome, rash, airway complications, cardiovascular instability, extravasation injury and extreme agitation.

Sample size

The sample size was based on published seizure cessation rates for phenytoin (50–60%) and levetiracetam (76–100%). A sample size of 140 participants in each group with a total of 183 events of convulsive status epilepticus cessation was required to achieve 80% power to detect an increase in convulsive status epilepticus cessation rates from 60% to 75%, with a 5% significance level two-sided log-rank test for equality of survival curves.

An adjustment for 10% loss to follow-up increased sample size requirements to a total of 308 randomised participants. However, as this did not occur, the final sample size was reduced to 286 participants, as approved by the trial oversight committees.

Statistical methods

The modified intention-to-treat population excluded patients who did not require second-line treatment and patients who did not give consent. It included all randomised, consented patients who received a second-line treatment in the group to which they were randomly allocated.

The safety population included all randomised, consented and treated patients in the group of the treatment that the patient actually received.

The primary analysis was by 'intention to treat'. A 5% level of statistical significance was used throughout and all results are presented with 95% confidence intervals. The primary outcome is a time-to-event outcome and was analysed using the log-rank test and Kaplan–Meier curves. Dichotomous outcomes were analysed using the chi-square test and presented with relative risks. Adjusted analyses were conducted using Cox proportional hazards models or logistic regression, as appropriate. Variables included in the models were determined from known prognostic factors. Serious adverse reactions are presented using descriptive statistics. Reasons for missing data, and rates and reasons for not obtaining deferred consent, were collected.

Consent study data analysis used descriptive statistics and chi-square test for trend. Qualitative data were analysed thematically. Data from study methods were analysed separately and then synthesised through constant comparative analysis.

Results

A total of 1432 patients were screened for eligibility. Four hundred and four participants were randomised ($n = 212$ levetiracetam, $n = 192$ phenytoin) and 311 participants ($n = 161$ levetiracetam, $n = 150$ phenytoin) required a second-line treatment. Valid consent was obtained for 286 participants ($n = 152$ levetiracetam, $n = 134$ phenytoin) who formed the modified intention-to-treat population. The safety population comprised 149 patients treated with levetiracetam and 137 patients treated with phenytoin.

Males constituted 49% (75/152) of the levetiracetam-treated group and 54% (72/134) of the phenytoin-treated group.

The median age was 2.7 (interquartile range 1.3–5.9) years in the levetiracetam-treated group and 2.7 (interquartile range 1.6–5.6) years in the phenytoin-treated group. Children aged < 2 years comprised 43% (65/152) and 40% (53/134) of the levetiracetam- and phenytoin-treated groups, respectively.

The presenting episode of convulsive status epilepticus was the first seizure in 45% (69/152) and 37% (49/134) of the levetiracetam- and phenytoin-treated groups, respectively.

Primary outcome

The episode of convulsive status epilepticus terminated in 106 (70%) and 86 (64%) participants of the levetiracetam- and phenytoin-treated groups, respectively. The log-rank test for time to seizure cessation was not statistically significant ($p = 0.20$), with the median time to seizure cessation (from randomisation) being 35 (interquartile range 20–not assessable) minutes and 45 (interquartile range 24–not assessable) minutes in the levetiracetam- and phenytoin-treated groups, respectively [unadjusted hazard ratio 1.20, 95% confidence interval 0.91 to 1.60, $p = 0.20$; adjusted (sex, weight and first seizure) hazard ratio 1.23, 95% confidence interval 0.92 to 1.63; $p = 0.16$].

Sensitivity analyses undertaken on the primary outcome confirmed the robustness of the results.

Secondary outcomes

Fifty-seven (38%) and 50 (37%) participants in the levetiracetam- and phenytoin-treated groups, respectively, received additional anticonvulsants (relative risk 1.01, 95% confidence interval 0.74 to 1.36; $p = 0.97$). Results were similar when restricted to the further management for the presenting episode of convulsive status epilepticus.

Forty-four (29.5%) participants in the levetiracetam group and 47 (35%) participants in the phenytoin group received rapid sequence induction because of ongoing convulsive status epilepticus (relative risk 0.83, 95% confidence interval 0.59 to 1.16; $p = 0.27$).

Ninety-seven (64%) participants in the levetiracetam group and 72 (54%) participants in the phenytoin group were admitted to critical care (relative risk 1.19, 95% confidence interval 0.97 to 1.45; $p = 0.08$).

Safety data were analysed by the treatment received. One hundred and thirty-two participants received levetiracetam only and 130 participants received phenytoin only. The remaining 24 participants received both treatments sequentially (i.e. 17 participants received levetiracetam followed by phenytoin and seven participants received phenytoin followed by levetiracetam).

Five serious adverse events were reported. Three serious adverse events occurred in two participants receiving phenytoin, one serious adverse event occurred in a participant receiving levetiracetam and one serious adverse event occurred in a participant who received both interventions. Four serious adverse events were resolved and the remaining serious adverse event occurred in a participant who died. The cause of death was catastrophic cerebral oedema and encephalitis that was unrelated to either treatment. This participant received levetiracetam followed by phenytoin. Two serious adverse events were assessed as having a causal relationship with treatment (one was classed as a serious adverse reaction and the other as a suspected unexpected serious adverse reaction). The serious adverse reaction was hypotension considered to be immediately life-threatening and the suspected unexpected serious adverse reaction was increased focal seizures and decreased consciousness considered to be medically significant. Both occurred in the same participant who was allocated and given phenytoin. The remaining serious adverse event occurred in a levetiracetam-treated participant who experienced a cardiorespiratory arrest owing to an obstructed endotracheal tube, which was considered unrelated to treatment.

In the consent study, 143 parents of randomised children (93 mothers, 39 fathers and 11 parents with missing information) completed a questionnaire and 30 (25 mothers and five fathers) were interviewed. Ten practitioners (four medical and six nursing) were interviewed, 36 (16 medical and 20 nursing) participated in one of six focus groups and 76 recorded trial discussions that were analysed.

Consent study findings showed how interactive site training, developed using pre-trial research and research without prior consent guidance, may significantly alleviate practitioner concerns about recruitment and consent in a challenging paediatric emergency medicine trial. Parental understanding of the EcLiPSE trial was enhanced when practitioners clearly described the trial aims, provided reasons for research without prior consent, explained the uncertainty about which intervention was best, provided a balanced description of both interventions, explained the randomisation process and provided an opportunity for questions. Multiple factors, including trial design, organisation and leadership, were found to both challenge and contribute to trial recruitment and conduct. The nested consent study provides valuable insight from parents and practitioners to inform the design and conduct of future trials in this setting, including a bespoke model to optimise discussions on recruitment into paediatric emergency medicine trials.

Conclusions

The two treatment groups were well balanced in terms of demographic profiles.

None of the primary and secondary outcome data demonstrated a statistically significant difference between levetiracetam and phenytoin. However, the direction of the results favoured levetiracetam in the primary outcome and most secondary outcomes (i.e. seizure cessation, time to seizure cessation, need for rapid sequence induction and serious adverse reactions). The findings favoured phenytoin in one secondary outcome (i.e. the need to be admitted to critical care).

The study demonstrated the acceptability of research without prior consent in the paediatric emergency setting, and how training and recruitment experience addressed clinicians' concerns about research without prior consent.

Recommendations for future research

A meta-analysis of all randomised controlled trial data on the use of levetiracetam as a second-line drug should be undertaken. This is one of the priorities of the EcLiPSE trial team. The role of sodium valproate and the sequential use of two anticonvulsants, specifically levetiracetam followed by phenytoin or levetiracetam followed by sodium valproate, could also be investigated. This would determine whether or not the use of two drugs reduces the need for third-line treatment with an anaesthetic, but without significantly prolonging convulsive status epilepticus.

Trial registration

This trial is registered as ISRCTN22567894 and European Clinical Trials Database EudraCT number 2014-002188-13.

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