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Title:

Novel Use of the ‘Photosensitivity Model of Epilepsy’ to Identify the Rapidity of Anti-Epileptic Drug (AED) CNS Penetration: Implications for future choice in iv Treatment of Status Epilepticus (SE).

The Methodological Question Being Addressed

Can ‘The Photosensitivity Model of Epilepsy’ biomarker methodology be adapted successfully to study the Pharmacokinetic/Pharmacodynamic (PK/PD) or *rapidity of CNS effect* and plasma concentrations of two *intravenously (iv)*-administered, chemically-related AEDs with fast CNS penetration in a standardized fashion?

Introduction (Aims)

The overall 40-70% efficacy rate for SE treatment by AEDs is still not considered optimal- better AEDs/treatments are needed. A key issue is *time* required to abort seizures. Standardized SE trials are very difficult to perform: why?-irregular occurrence, differences in SE severity, time to hospital and AED(s) already given and *limitations on AED iv infusion-times*.

The human Phase-IIa “Photosensitivity Model in Epilepsy” has been successfully utilized to identify the preliminary efficacy of single *oral* doses of potential new AEDs in epilepsy patients for years. The conventional model consists of repeated-hourly-EEG photosensitivity measures- *biomarker of epileptic activity*-comparing a baseline placebo day (placebo, Day 0) with a single oral dose of AED (Day 1) over 8-12 hrs within the same patient on separate occasions, followed by a 3rd placebo day (duration of AED effect). Results are known of both Levetiracetam-(LEV) and n-propyl derivative, brivaracetam-(BRV) being separately tested after per-oral administration in this model. Both suppressed the EEG photosensitivity response at hr 1. However, for iv status epilepticus prevention, time to effect lies in the order of minutes after iv-infusion. In order to assess differences in time to effect (efficacy) of iv neuroactive AEDs, the Model’s procedure needs to be repeated every few minutes. The conventional ‘Model’ involves intermittent (regular, over half- or hourly intervals x 12hr) blood sampling for AED concentration performed simultaneously with photic-induced EEG. These EEG measurements are time-intensive, requiring 7-10 minutes of operational activity (three eye conditions + separate flash frequencies, from 2- 60 Hz) per photic-stimulation-result. ‘The Model’ works for orally administered AEDs, but the methodology has not yet been applied to AEDs given intravenously where an EEG effect is anticipated within 30 minutes. We needed to adapt ‘The Model’ to compare two iv AEDs in the same patient.

Methods

The model needed to become more time efficient. We adapted the ‘Model’ in three ways:

- i. by only studying the AED-produced change in each volunteer-patients’ EEG *upper limit/threshold* only (see Reed & Kasteleijn ISCTM poster),

- ii. by choosing to limit 3 eye conditions to the patient's "best one", based upon screening photosensitivity data;
- iii. by eliminating some high Hz measurements, based upon each patient's screening photosensitivity data.

With these adaptations to the conventional 'Model', we devised a prospective, randomized, crossover, controlled *iv 2-hour* study using frequent measurements of the evoked photo-paroxysmal EEG response (PPR) as a PD efficacy endpoint. An *intra*-patient comparison of three PD metrics (time to effect, time to peak effect, and magnitude of effect), in adult photosensitive epilepsy patients from time zero up to two (2.0) hours after a 15-minute zero-order infusion Levetiracetam (LEV) 1500 mg versus an equipotent dose of Brivaracetam (BRV) 100 mg, two separate occasions, in random, crossover, double-blind fashion (n = 8 patients).

Results

We adapted 'The Model' such to be able to elicit data to compare the *rapidity* of effect of two similar AEDs given *intravenously*. The adaptation of 'The Model' has worked in the first patients being investigated (comparative AED EEG data generated).

Conclusion

Adaptation of the standard "Photosensitivity Model" should allow the determination of differences (if it exists) in time to CNS entry (effect) of *iv* infusion of two nearly identical AEDs. Data obtained in such a manner could help SE treatment algorithms.

Disclosures:

Two authors (RCR & DKNT) wrote a full, Investigator-Initiated, Phase-4 Study plan (IIS) with adaptation to the standard photosensitivity model to be able to compare *iv* LEV vs. BRV for time to entry CNS; UCB has funded the actual AED trial.