Novel Use of the 'Photosensitivity Model of Epilepsy' to Identify the Rapidity of Anti-Epileptic Drug (AED) CNS Penetration

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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 Standardized Status Epilepticus (SE) treatment by AEDs is still not considered optimal- better AEDs/treatments are needed. A key issue is *time* required to abort seizures. 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 (Yuen & Sims, *Seizure* 2014). 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 frequent photic-induced EEG measurements. Such 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 similar 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 each patient's screening photosensitivity data;

iii. by eliminating some high Hz measurements, based upon each patient's screening photosensitivity data.

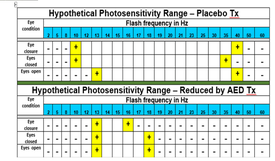
With these adaptations to the conventional 'Model', we devised a prospective, randomized, crossover, controlled *iv 2-hour* study using frequent measurements of the evoked photo-paroxysmal EEG response (PPR) as a PD efficacy endpoint. An *intra*-patient comparison of three PD metrics (time to effect, 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 / DISCUSSION

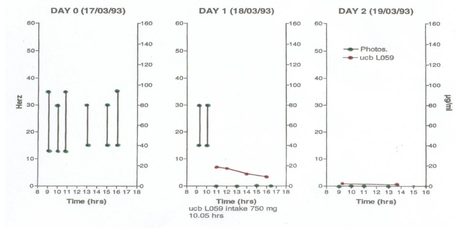
- **Figure 1a** depicts a photosensitive patient prepared for a 21-channel EEG, with photic stimulator in place for the conventional Photosensitivity Model prior to AED administration.
- **Figure 1b** depicts comparison of a hypothetical patient's photosensitivity range for baseline placebo day (top panel) vs. a novel AED dosed on a subsequent day (bottom), showing a reduced range in PPR (compare + signs, indicating a presence of a PPR, highlighted in yellow).
- **Figure 2a & b** shows the PD effect of 2 select AEDs, levetiracetam (LEV) & brivaracetam BRV), over time after oral intake of a single dose, plus onset & duration of AED effect on PPR; both show large declines in the upper photosensitivity limit (conventional 'Model' methodology over 12hr/day); **Figure 2c** depicts a patient's generalized PPR on EEG in response to photic stimulation.

'1a'

'1b'



'2a'



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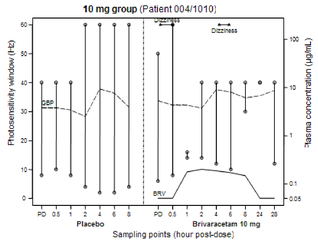
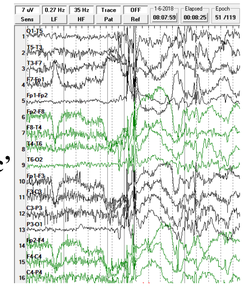


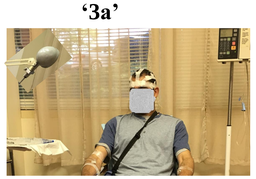
'2c'



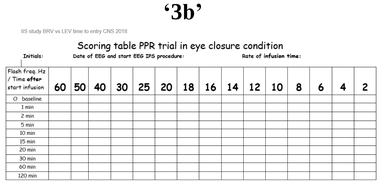
Patient with photosensitivity, during eye closure, @ 30 Hz flashing white light--- EEG shows epileptiform discharges and myoclonic jerks.

- 'The Photosensitivity Model' is conventionally used over 3 days, 12 hr/day, with intermittent photic stimulation occurring hourly, for the evaluation of new AEDs with single oral AED doses. We adapted the 'Model' to be able to acquire serial data over a 2-hr period, in order to compare the *rapidity* of EEG effect of two similar AEDs, LEV & BRV, given *intravenously over 15 min*.
- **Figure 3a** shows a photosensitive JME patient with epilepsy being prepared for study via the adapted 'Model' (21-channel EEG, 2 iv lines inserted into antecubital fossa (1 for *iv* AED administration, the other for serial blood sampling for [LEV] or [BRV] concentration determination); serial blood sampling coincides with photic stimulation times. **Figure 3b** shows the new PPR scoring table, high Hz 1st, with serial photic measurements occurring just minutes apart over 2 hours for *iv*-administered AEDs. **Figure 3c** shows the treatment flowchart for our double-blind, randomized, crossover study of LEV vs. BRV in patients.

'3a'



'3b'



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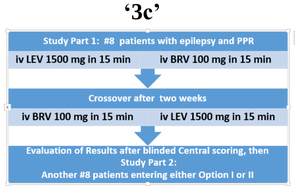

•The 3 way adaptation of 'The Model' (see Methods) as a biomarker of AED effect has worked in the first few patients being investigated in a study of the comparative use of iv-administered AEDs (comparative AED EEG data generated).

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) to compare iv LEV vs. BRV; UCB has funded it.