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Brivaracetam or levetiracetam in status epilepticus?: Lessons from the photosensitivity model

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ABSTRACT

First, a short history is given of the use of the EEG as a biomarker of efficacy in anti-seizure medication (ASM) development. The generalized epileptiform EEG response to Intermittent Photic Stimulation (IPS), the photoparoxysmal EEG response or PPR, in particular, is a reliable reproducible measure since the 1950s.

Over time, a "Photosensitivity Model", testing within the same patients the impact of potential new oral ASMs, along with dose-ranging data, on PPRs, has been developed successfully. The classical Photosensitivity Model consists of IPS and blood sampling for ASM measurement performed hourly between 8 AM and 5 PM over three consecutive days. This single-blind, placebo-controlled, pharmacokinetic-pharmacodynamic (PK/PD) Model is now commonly utilized as a Proof-of-Concept Phase 2a trial.

For Generalized Tonic-Clonic Status Epilepticus (GTCSE), it is especially relevant to know the time for CNS entry and effect minutes after i.v. ASM treatment, since "time is brain". We, therefore, adapted successfully the Model to a time-efficient Model with the determination of photosensitivity ranges in minutes after equivalent doses of iv brivaracetam (BRV) and levetiracetam (LEV). This modified design allows one to monitor the time to CNS effect (*i.e.,* PPR elimination) of a quickly-acting FDA-approved ASM given i.v., a crucial element in status epilepticus treatment. This paper was presented at the 8th London-Innsbruck Colloqium on Status Epilepticus and Acute Seizures held in September 2022.

1. Brief history of photosensitivity employed to evaluate anti-seizure medicines (ASMs)

"*The epileptic seizure is only the portion of the tree above the ground, the visible expression of the disturbance in the brain. The EEG lays bare the roots. By the use of this technique, one can, in the laboratory, make a running record both of clinical seizures and of the lesser disturbances which give no clinical evidence of their presence; one can study the effect of various drugs on the seizure pattern*" as quoted from the lecture given by William Lennox in 1936 in Kansas City [1]. He and colleagues indeed showed the suppressive effect on the spike-and-wave discharges in the EEG of both intravenous (i.v.) phenobarbital and i.v. sodium bromide in the same patient with frequent absence seizures and concomitant spike-and-waves (*i.e.,* epileptiform EEG discharges) on baseline EEG. Ten years later Cobb [2] showed that intermittent photic stimulation (IPS) could evoke those epileptiform discharges and related absences in the EEG laboratory independent of the variability in the occurrence of absence seizures; hyperventilation increases the frequency of absence but is yet dependent on the performance by the child.

The very first drug trial with IPS [3] tested the effect of an analog of ethosuximide, i.v. tridione [4], by using the IPS-evoked epileptiform discharges (photoparoxysmal EEG discharges, or PPR) as a biomarker for effect. Bickford [3] found that the PPR disappeared when tested at the same previously epileptogenic flash frequency in a particular child two min post-i.v. tridione. Soon afterwards, many EEG studies in Europe and the USA were performed on a variety of patients, appreciating the fact that discharges could be evoked systematically and repeatedly, leading to a fixed set of flash frequencies for which a patient is sensitive---the so-called "photosensitivity range". This range is also positively correlated with the risk

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of occurrence of seizures in daily life, wherein a patient with a larger photosensitivity range is more likely to have a convulsion [5,6]. Determination and periodic monitoring of the individual epileptic thresholds has been shown to prevent the occurrence of generalized-tonic-clonic seizures (GTCS) [5,6].

Over time, a "Photosensitivity Model", testing the impact of the potential of new oral anti-seizure medicines (ASMs), along with dose-ranging data, on electroencephalographic PPRs produced by IPS, has been developed successfully; this single-blind, placebo-controlled, pharmacokinetic-pharmacodynamic (PK/PD) model is now commonly utilized as a Proof-of-Concept Phase 2A trial in the early development of new ASMs [6–8]. Based on the fact that when photic stimulation is performed in a standardized manner [6,10] the EEG response of photosensitive epilepsy patients is quantifiable and surprisingly consistent when assessed at hourly intervals over a waking day. The classical Photosensitivity Model consists of IPS and blood sampling for ASM measurement performed hourly between 8 AM and 5 PM over three consecutive days: on Day 1 (baseline Day) a placebo is given at hour 8.30 AM and on Day 2 (ASM test day) a single oral dose of the ASM under investigation is given at the same time as the placebo on the previous day. Day 3 is used to learn about the duration of the ASM effect. Dose-ranging occurs in separate groups of four patients each. Reduction of the photosensitivity ranges over time shows the time of onset of the ASM effect and its duration, all in combination with ASM concentration measurements [8].

Small studies with i.v. diazepam (DZP) have also been performed using the PPR as a biomarker: 5 or 10 mg (10 mg in adults) given over a period of 1–2 minutes suppressed the PPR in all patients of two similar types of studies [6,9]. Booker [9] found that in PPR-positive patients that the i.v. DZP suppressive effect lasted from 15 to 60 min and was associated with peak plasma DZP concentrations until it dropped below 0.6 mg/L. The results on spontaneous discharges in other patients gave a much more variable result.

It deserves mention that a revised Photosensitivity Model has been applied, as a Phase 2A proof-of-concept study in patients with epilepsy plus photosensitivity, to determine the efficacy and effective dosing range of staccato-inhaled alprazolam for the treatment of acute repetitive seizures [11], with the hope of preventing Generalized Tonic-Clonic Status Epilepticus (GTCSE). Its' success has propelled inhaled-staccato alprazolam towards more definitive Phase 3 trials (see ClinTrials.gov).

2. The most recent robust study of benzodiazepine-refractory established GTCSE

Many ASMs are on the market and several are being used in status epilepticus treatment: however, which choice is best for timely efficacy? A recent double-blind, well-conceived, and conducted study [12] comparing three ASMs, i.v. levetiracetam vs i.v. valproate vs i.v. fosphenytoin, in adult patients with benzodiazepine-refractory established GTCSE, found no statistically significant differences in seizure cessation and improved alertness by 60 minutes (Table 1). Less than a 50 % response rate was achieved despite maximal mg/kg i.v. ASM doses being are administered over 10 minutes. This trial was stopped early by the monitoring board due to the futility of finding any differences among treatments! One may deliberate over whether or not this represents the best we can do for benzodiazepine-refractory GTCSE treatment.

3. Can the "Model help to identify other ASMs useful in the treatment of GTCSE?

For GTCSE, it is especially relevant to know the time for CNS entry and effect *minutes* after i.v. ASM treatment, since "time is brain" [13]. Since levetiracetam (LEV), valproate and fosphenytoin have essentially been found to be equivalent in the treatment of GTCSE, and only effective in less than half of patients [12], clinicians must look to other i.v. ASMs for prompt resolution of GTCSE. Studies show that brivaracetam (BRV) has desirable physical and chemical attributes over LEV: BRV has ≥10x greater potency vs LEV [14,15], higher lipophilicity [15], and a 10x greater affinity to the SV2A-binding site (pK_i = 7.1) compared to LEV (pK_i = 6.1) [16,17]. Furthermore, BRV has been shown to have faster brain uptake than LEV via a positron emission tomography (PET) study in human volunteers [18] (see Table 2).

We were therefore interested in comparing in the photosensitivity model the "old" standard levetiracetam (LEV) with the more recently introduced brivaracetam (BRV), both analogs of piracetam and both working on SV2A brain receptors. LEV [19] and BRV [20] had been separately tested in the classic photosensitivity model, at the earliest time points of 0.5 and 1 hour after *oral* intake, revealing a statistically greater effect of BRV in PPR elimination (**see** Fig. 1). We, therefore, the Model to make a head-to-head comparison of i.v. LEV and i.v. BRV in the same photosensitive patients in the same setting, thus eliminating the influence of factors other than the PPR range. Specifically, we modified the classical Model from hourly IPS observations to one that could be conducted every 1 minute, by limiting IPS testing to each patient's individualized "best or most sensitive" eye condition, by examining high threshold range reduction only, and by starting IPS testing at one-step above the Hz threshold known to be provocative in a patient [8]. Thus, this converted, time-efficient Model allows one to monitor time to CNS effect (*i.e.,* PPR elimination) of a quickly-acting FDA-approved ASM given i.v., a crucial element in status epilepticus treatment, since "time is brain" [13]. A Visit & Procedure Flowsheet depicts how our compressed IPS technique, described above, can be used rapidly and sequentially every minute/few minutes when

Table 1
Salient results[¶] from a prospective, randomized, double-blind trial of three major ASMs in benzodiazepine-refractory GTCSE-(USA Established Status Epilepticus Treatment Trial-ESETT [12]).

Study i.v. ASMs:	Levetiracetam	Valproate	Fosphenytoin
Variable:			
mg/kg i.v. dosing over 10 min:	60	40	20
Maximal dose, mg:	4,500	3,000	1,500
Patient N with Outcome, Intent-to treat:	68	56	53
1° outcome: % Patients achieving 1^0 outcome (clinical seizure cessation + ↑ in consciousness in <1 hr without other ASM treatment):	**47 %** (39–55 %)[§]	**46 %** (38–55 %)[§]	**45 %** (36–54 %)[§]
Median time to seizure cessation from i.v. start (min):	10.5	7.0	11.7
% seizure recurrence (1–12 hrs post-infusion):	10.7	11.2	11.2

[¶]All results listed are adapted from ESETT Table 2.
[§] 95% credible interval.

Table 2
PET Study [18] Showing Faster CNS Entry for BRV vs LEV (via SV2A Occupancy).[¶]

	Corrected drug-entry half-time (min), showing BRV is faster than LEV		
ASM, mg dose	Mean value	± SD	Total # patients, n
LEV, 1500 mg x6 patients	20.45	5.7	6
BRV, 100 mg x4 patients	9.4	8.1	7
BRV, 50 mg x1 patient			
BRV, 200 mg x2 patients			

[¶]Data adapted from Finnema's Table 1 [18].

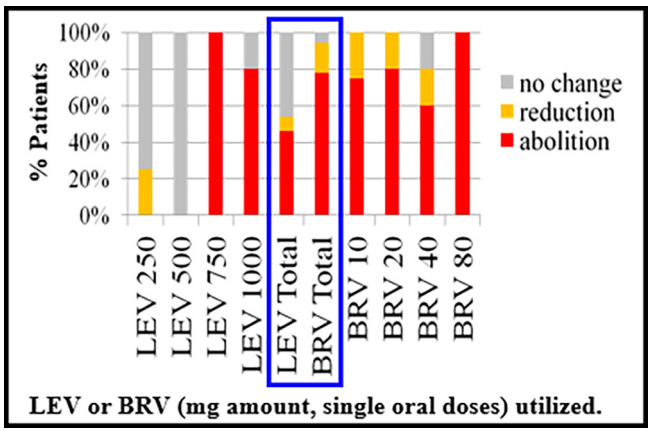

Fig. 1. Comparison of levetiracetam (LEV) and brivaracetam (BRV) in two distinct Phase 2A dose-ranging studies (Ref. # 12 & #13, respectively) showing the effect on PPR in the Photosensitivity Model (LEV, n = 12; BRV, n = 18 patients). At equipotent mg single oral doses, BRV produced a greater (number and) percent of patients with PPR elimination vs LEV (p = 0.0251, Fisher's Exact Test, **blue-box insert**, adapted from [8]).

evaluating i.v. ASMs in a head-to-head trial (**see** Fig. 2**)**. Based upon chemical and PET evidence that BRV distinguishes itself from LEV, plus with a revised, sleek Model that could deliver very frequent IPS testing, we sought to directly compare two i.v. ASMs in the Model for their rapidity in CNS penetration.

We conducted a double-blind, randomized, direct comparative crossover trial [21] of equipotent mg doses of i.v. 1,500 mg LEV vs 100 mg i.v. BRV, using this amended Model, in two parts (both a 15-minute linear infusion and separately in a 5-minute infusion, in eight patients with epilepsy plus photosensitivity); comparison of these two ASMs for time to elimination of PPR on EEG was the pharmacodynamic biomarker. The median intra-patient BRV:LEV *ratio* value for time to PPR elimination for combined data (n = 16) was 0.39 (95 % CI: 0.16 to 0.91), p = 0.039, *i.e.* i.v. BRV was 61 % faster than i.v. LEV (Fig. 3). In terms of absolute time to EEG PPR elimination, when combining data for Parts I & II (n = 16 patients), i.v. BRV 100 mg had a median 2 minutes CNS entry time compared to 7.5 minutes for i.v. LEV 1,500 mg, a difference of 5.5 minutes faster in favor of i.v. BRV. Grouping responders into blocks of time, the majority of i.v. BRV patients had a faster time, 2–5 min, compared to i.v. LEV (Table 3).

4. Summary

The Photosensitivity Model has been employed frequently and to great advantage in early Phase 2A, Proof-of-Concept-evaluation of oral ASMs in the treatment of seizure disorders. Its modification to rapidly and sequentially test IPS in photosensitive epilepsy patients has been successfully demonstrated. Clinicians must and will move forward in their study of benzodiazepine-refractory GTCSE; while ESETT demonstrates equivalence among a top tier of i.v. ASMs, namely levetiracetam, valproate, and fos-

DAY	-21 to -1 Visit 1	0	1 and 15 (+14 days) Visit 2 and 3										Up to two weeks post visit 3
	Screening	Admitted	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	Final visit Day
Time min from baseline	Morning	-60	0	+1	+ 2	+5	+10	+15	+20	+30	+60	+120	
Signed informed consent	✖												
Inclusion/exclusion criteria	✖		✖										
Pregnancy Test	✖		✖										✖
Medical history	✖												✖
Demography	✖												
Physical examination	✖												✖
Vital Signs	✖		✖						✖	✖	✖	✖	✖
EEG-IPS Assessment	✖		✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	
Biochem, hematology	✖		✖										✖
Drug levels LEV /BRV			✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	
Levels Co-AEDs	✖		✖									✖	
Administration LEV/BRV			✖										

Fig. 2. Procedure flow sheet depicting an amended 'Model' set for rapid, repeated IPS testing for PPR on EEG. Blood samples for plasma ASM concentration were drawn concurrently for pharmacodynamic measurements (see **red boxed 'x' marks below**).

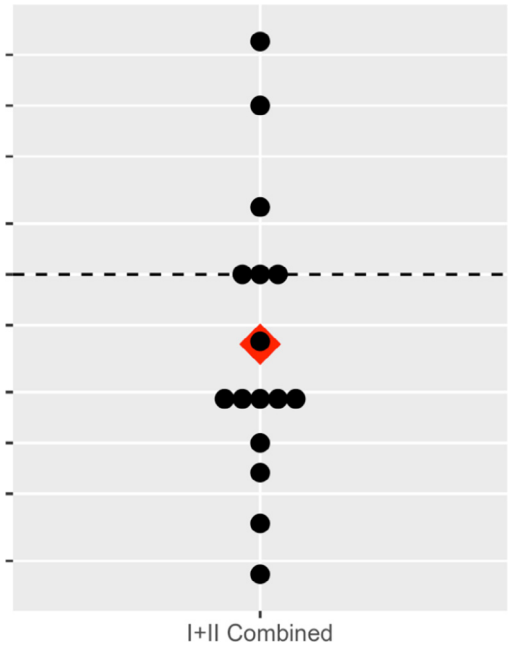

Fig. 3. Individual BRV: LEV intra-patient time ratio values are denoted by the black dots (●) and the median by the red diamond (♦). A BRV:LEV time ratio of unity (value = 1.0, dotted horizontal line) means no difference in time to PPR elimination on EEG between the two ASMs administered i.v.; a ratio value <1.0 indicates a faster time to PPR elimination for BRV over LEV, while a value >1.0 denotes that LEV was faster than BRV. When data for separate Parts I & II are combined (n = 16), the median intra-patient BRV:LEV ratio value for time to PPR elimination = 0.39 (95 % CI: 0.16 to 0.91; $p = 0.039$). At the equipotent doses used, i.v. BRV is statistically 61 % faster than i.v. LEV. Data depicting results for Parts I & II separately is shown and detailed elsewhere [21].

Table 3
Number and Percent of Patient Episodes with PPR elimination on EEG for i.v. BRV vs i.v. LEV at ≤2, 5, and ≥10-minute time-points in patients with photosensitive epilepsy. Grouping responders into blocks of time, the majority of i.v. BRV patients respond in 2–5 min.

ASM	Number of occasions (% of patients) with PPR elimination at designated time points:		
(n observations, Parts 1&2)	≤2 min	5 min	≥10 min
i.v. BRV, 100 mg (n = 16)	11 (69 %)	3 (19 %)	2 (12 %)
i.v. LEV, 1,500 mg (n = 16)	4 (25 %)	4 (25 %)	8 (50 %)

Adapted and modified from Table 3 [21].

phenytoin, ultimately, the "glass is half-full", since the response for all three ASMs was less than 50 %. Other i.v. ASMs and/or re-purposed drugs need to be studied in GTCSE. In the next major trial of multiple i.v. ASMs to be compared for efficacy in GTCSE, i.v. brivaracetam should definitely be considered, as evidenced by data via both PET data and the 'Photosensitivity Model'. This Model should be utilized to help define and characterize the future choices of available i.v. ASMs for GTCSE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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