Seizure 23 (2014) 490–493

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Short communication

How predictive are photosensitive epilepsy models as proof of principle trials for epilepsy?

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ARTICLE INFO

Article history:
Received 6 January 2014
Received in revised form 4 March 2014
Accepted 19 March 2014

Keywords:
Epilepsy
Photosensitive
Proof of principle
Drug development

ABSTRACT

Purpose: Human photosensitive epilepsy models have been used as proof of principle (POP) trials for epilepsy. Photosensitive patients are exposed to intermittent photic stimulation and the reduction in sensitivity to the number of standard visual stimulation frequencies is used as an endpoint. The aim of this research was to quantify the predictive capabilities of photosensitive POP trials, through a survey of current literature.
Methods: A literature search was undertaken to identify articles describing photosensitive POP trials. Minimally efficacious doses (MEDs) in epilepsy were compared to doses in the POP trials that produced 50–100% response (ED_{50-100}). Ratios of these doses were calculated and summarised statistically.
Results: The search identified ten articles describing a total of 17 anti-epileptic drugs. Of these, data for both MED and ED_{50-100} were available for 13 anti-epileptic drugs. The average ratio of MED to ED_{50-100} was 0.95 (95% CI 0.60–1.30). The difference in MED to ED_{50-100} ratios between partial epilepsy (0.82) was not significantly different from that of generalised epilepsy (1.08) ($p = 0.51$).
Conclusion: Photosensitive POP trials are a useful tool to quantitatively predict efficacy in epilepsy, and can be useful as early and informative indicators in anti-epileptic drug discovery and development.

1. Introduction

Proof of principle (POP) trials are used early in drug development, typically after phase 1 or early in phase 2, and aim to give an early read out of potential efficacy. In the area of epilepsy, biomarkers are not readily available and mechanisms of action may not be fully elucidated for some classes of drugs. Thus, POP trials have significant potential in anti-epileptic drug (AED) development by providing early indicators of efficacy, improving decision-making and potentially reducing the cost of Phase 2/3 failures.

POP trials for epilepsy include inter-ictal discharges, transmagnetic cranial stimulation or photosensitive epilepsy, of which the first two have been associated with variable responses or providing limited data for the effects of AEDs.[1] Photosensitive POP trials can be a reliable early indicator of pharmacodynamic activity for a number of novel AEDs.[2–5] In these trials, photosensitive epileptic patients are exposed to intermittent photic stimulation and the provocation of paroxysmal discharges is monitored. The outcome measured is the number of standard visual stimulation frequencies to which the patient is sensitive, and response can generally be classified as complete abolishment of sensitivity, partial or none.

Since photosensitive POP trials have already been shown qualitatively to be an early indicator of pharmacodynamic activity, the aim of this research was to take a step further to quantify the predictive capabilities of photosensitive POP trials, in order to better characterise the utility of such trials in epilepsy drug development. This was done through a survey of current literature reporting results on photosensitive POP trials.

2. Materials and methods

A literature search was undertaken in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) using four different combinations of keywords. The first search used "photosensitive" and

Abbreviations: POP, proof of principle; MED, minimally efficacious dose; ED_{50-100}, doses at which 50–100% of patients had positive response; AED, anti-epileptic drug.

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http://dx.doi.org/10.1016/j.seizure.2014.03.011
1059-1311/

Table 1
Literature survey search strategy and results.

Search number	Keywords	No. of e-articles ahead of print	Filters used	No. of results retrieved	No. of articles included
1	Photosensitive, epilepsy	12	Clinical trial	19	5
2	Photosensitivity, epilepsy	20	Clinical trial	38	2[a]
3	Photosensitive, epilepsy, model	0	Human	49	3[a]
4	Photosensitivity, epilepsy, model	0	Human	21	0[a]

[a] Duplicate articles from previous searches were not included.

"epilepsy", and the second replaced the keyword "photosensitive" with "photosensitivity". This was then repeated for the third and fourth searches by adding the term "model". Search results were sorted by recently added articles and all e-publications ahead of print were separately identified prior to the addition of filters of "clinical trial" and/or "humans" to the results. Articles describing photosensitive POP trials using a single dose of AED were included, whilst articles describing clinical trials for non-drug treatment or chronic treatment of photosensitive epilepsy with AEDs were excluded.

Minimally efficacious doses (MEDs) for treatment of epilepsy (partial, generalised or both) for approved AEDs described in the POP trials were obtained from the respective drug labels. For non-approved AEDs, a search was conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) using the drug name as keyword and limited to clinical trials. MEDs were determined from double-blind, placebo controlled trials in partial or generalised epilepsy where significance from placebo was observed. Where more than one trial was available for a particular drug, the average across the lowest efficacious doses in each trial was obtained. In the POP trials, efficacious doses were defined as dose levels in which 50–100% of patients had a positive response (ED_{50-100}), where a response was considered to be either a complete abolishment or a significant partial decrease in sensitivity to standard visual frequencies. No attempt was made to distinguish between these two types of positive responses since small numbers of patients (majority of trials had 4–6 patients per dose level, range 1–14) were typically tested at each dose level.

For each AED, the ratio of MED to ED_{50-100} was calculated when both values were available, since efficacy data was not available for all drugs used in photosensitive POP trials. The ratios were described by summary statistics. No weighting factor was included for study size and/or quality since the conduct of most of these trials were similar using small numbers of patients.

3. Results

In total, ten articles were identified that fit the inclusion criteria.[2–11] The results of the literature search are described in Table 1. Of the ten, eight described positive results only, one described an unexpected increase in photosensitive epilepsy when patients were given Org 6370,[6] and another described mixed results with two marketed AEDS (carbamazepine and levetiracetam).[10] These ten articles described the use of a total of 17 drugs in photosensitive epilepsy POP trials, however efficacy data (MED) was only found for 13 drugs, since some drugs had not undergone phase 2/3 trials or the trial results had not been reported at the time of conducting the search.

Of the 13 AEDs, six were indicated in partial seizures, three in generalised seizures and three in both types. The doses investigated in the POP trials were either close to, or encompassed the MED for epilepsy. The results show that across the AEDs, the average ratio of MED to ED_{50-100} was 0.95 (95% CI 0.60–1.30) with all ratios contained within 2-fold. The difference in MED to ED_{50-100} ratios between partial epilepsy (0.82, 95% CI 0.46–1.18) was not significantly different from that of generalised epilepsy (1.08, 95% CI 0.60–1.56) ($p = 0.51$). The ratios of MED to ED_{50-100} for each AED are reported in Table 2.

Table 2
Anti-epileptic drugs investigated in photosensitive POP trials and the comparisons to minimally efficacious doses in epilepsy.

AED	Doses investigated in POP trial (mg)	ED_{50-100} (mg)	MED (type of seizure indicated)[a]	Ratio MED:ED_{50-100}[b]	Reference
Diazepam	5	5	2 mg (adjunct in convulsive disorders)	0.4	Binnie et al.[5]
Sodium valproate	600, 900	600	600 mg (partial)	1	
Mephenytoin	400	400	200 mg (generalised)	0.5	
Progabide	1200–1800, 2700	1200–1800	1800 mg[c] (partial + generalised)	1.2	
Ethosuximide	400	400	500 mg (generalised)	1.3	
Primidone	500	500	750 mg (generalised)	1.5	
Lamotrigine	120, 240	240	225 mg (partial + generalised)	0.9	
Nafimidone	200, 400	400	600 mg[d] (partial)	1.5	
Carbamazepine	400	400	800 mg (partial + generalised)	2	
Loreclezole	100–110, 150	100	12.5 mg[e] (partial)	0.13	Overweg et al.[8]
Levetiracetam	250, 500, 750, 1000	500–1000	1000 mg (partial)	1.3	Kastelijn-Nolst Trenité at al.[2] and French et al.[10]
Carisbamate	500, 750, 1000	500–1000	350 mg[f] (partial)	0.4	Kastelijn-Nolst Trenité et al.[3]
Brivaracetam	10, 20, 40, 80	10	5 mg[g] (partial)	0.5	Kastelijn-Nolst Trenité et al.[4]

[a] Minimally efficacious doses in epilepsy obtained from professional monographs on www.drugs.com unless otherwise stated.
[b] If ED_{50-100} is presented as a range of values, the average value is used for ratio calculations.
[c] Average calculated from Martinez et al.,[12] de Pasquet et al.[13] and Loiseau et al.[14]
[d] Obtained from Treiman et al.[15]
[e] Obtained from Rentmeester et al.[16]
[f] Average calculated from Faught et al.[17] and Sperling et al.[18]
[g] Obtained from French et al.[19]