Seizure 24 (2015) 21–27

Contents lists available at ScienceDirect

Seizure

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

Can pentylenetetrazole and maximal electroshock rodent seizure models quantitatively predict antiepileptic efficacy in humans?

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ARTICLE INFO

Article history:
Received 26 August 2014
Received in revised form 12 November 2014
Accepted 17 November 2014

Keywords:
Epilepsy
Maximal electroshock
Pentylenetetrazole
Drug development
Seizure model
Translational models

ABSTRACT

Purpose: Pentylenetetrazole and maximal electroshock rodent seizure models are commonly used to detect antiepileptic efficacy in drug development. The aim of this research was to evaluate the predictive capabilities of pentylenetetrazole and maximal electroshock models in estimating human exposures required for antiepileptic efficacy through a survey of current literature.
Methods: A literature search was undertaken to identify articles describing pentylenetetrazole or maximal electroshock models in rat or mice, where at least one of nine pre-selected antiepileptic drugs based on evidence of efficacy were used. Exposures at the median doses of the approved human dose range for these drugs were compared to exposures at doses that inhibit maximal response by 50% (ED50s) from the pentylenetetrazole and maximal electroshock models. Ratios of the human to rodent exposures were calculated and summarised statistically and graphically.
Results: Across the nine antiepileptic drugs investigated, the average (standard deviation) ratio of exposures comparing the median human efficacious dose to mice ED50 dose was 1.4 (3.9) for the pentylenetetrazole model and 3.8 (3.1) for the maximal electroshock model. In the rat, ratios in the maximal electroshock and pentylenetetrazole model were 4.1 (2.1) and a range of 1–2, respectively.
Conclusion: Based on the nine antiepileptic drugs investigated, the pentylenetetrazole model appeared to predict human exposures more accurately than the maximal electroshock model. There did not appear to be differences between rat and mice in either of the seizure models, therefore both species could be used equally. Both the pentylenetetrazole and maximal electroshock models are useful tools in screening compounds in early drug discovery.

1. Introduction

In the discovery phase of drug development, in vivo pharmacology experiments in animals are commonly used alongside in vitro experiments to screen for efficacy and early detection of activity. In the area of epilepsy, several nonclinical pharmacology models are available, which generally involve the application of a chemical or electrical stimulus to invoke seizures in rodents. The ability of an investigative drug to prevent these seizures is then observed. In an effort to facilitate the discovery of new antiepilepsy drugs (AEDs), the National Institutes of Health (NIH) runs an anticonvulsant screening program,[1] where submitted potential anticonvulsants undergo a list of screening tests in various animal seizure models.

Two commonly used in vivo nonclinical pharmacology seizure models in the NIH program – the pentylenetetrazole seizure (PTZ) model and the maximal electroshock seizure (MES) model – have been in use for decades and are currently still in use. In the PTZ model, the convulsant chemical pentylenetetrazole is injected subcutaneously into the rodent to produce clonic seizures. The ability of a test compound at different pretreatment doses/times to raise the seizure threshold and protect the animal from exhibiting a clonic seizure is observed, usually for 30 min after injection of PTZ. With the MES seizure model, an alternating current is delivered through corneal electrodes to induce a seizure in rodents.

Abbreviations: AED, antiepileptic drug; AUC, area under the plasma concentration vs time curve; CBZ, carbamazepine; ED50, dose that inhibits maximal response by 50%; FDA, Food and Drug Administration; GBP, gabapentin; ILAE, International League against Epilepsy; LTG, lamotrigine; MED, median effective dose; MES, maximal electroshock; NIH, National Institutes of Health; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PTZ, pentylenetetrazole; TPM, topiramate; VGB, vigabatrin; VPA, valproate.

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http://dx.doi.org/10.1016/j.seizure.2014.11.006
1059-1311/

Again, the ability of a test compound at different pretreatment doses/times to prevent the spread of seizure discharge and protect the animal from exhibiting hindlimb tonic seizures is observed. PTZ models are often associated with absence seizures whilst MES models are associated with general tonic-clonic seizures. In both models, a dose that inhibits maximal response by 50% (ED50) is often calculated from these experiments.

We have previously shown that photosensitive proof of principle trials in human can predict human antiepileptic efficacy,[2] and therefore can be a useful tool in drug development. Prior to first human dose testing, data from animal pharmacology models already available can potentially be used to inform and predict exposures in humans required for efficacy. The aim of this research was to evaluate whether preclinical seizure models – specifically the PTZ and MES rodent models – can be early predictors of human exposures required for antiepileptic efficacy. This was performed through a survey of current literature reporting ED50 results from commonly prescribed AEDs.

2. Materials and methods

In order to streamline the list of AEDs, only those that presented with good evidence of efficacy were selected according to the International League Against Epilepsy (ILAE) treatment guidelines.[3] Drugs with the highest levels of evidence for efficacy included carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), topiramate (TPM) and vigabatrin (VGB). A literature search was then undertaken in Medline using key words of "PTZ seizure" or "MES seizure", "mice" or "rat" and the respective drug name. Articles in English published before December 2012 describing an ED50 value with single dose treatment with any of the AEDs listed above in a PTZ or MES model were included. The average value of the rodent ED50s obtained from the various literature sources was then calculated.

The range and median effective doses (MEDs) in humans for the nine drugs listed above in the treatment of epilepsy were obtained from the individual Food and Drug Administration (FDA) approved drug labels. In order to account for species differences in disposition of the AEDs between rodents and humans, doses were converted to exposures for comparison. Exposures expressed as area under the plasma concentration time curve (AUC) for human MED and rodent ED50 were calculated using the following equation:

$$\mathrm{AUC} = \frac{\mathrm{Dose\ (human\ MED\ or\ rodent\ ED50)}}{\mathrm{CL}}$$

The human and rodent plasma clearance (CL) values for each AED were obtained from the FDA approved drug labels, FDA reviews, or literature.[4–12] Since mice pharmacokinetics were not commonly reported, mouse clearance where unavailable was scaled down from rat clearance using simple allometry principles with the following equation:

$$\mathrm{CL_{mouse}} = \mathrm{CL_{rat}} \times \left(\frac{\mathrm{Weight_{mouse}}}{\mathrm{Weight_{rat}}}\right)^{0.75}$$

The standard weights used for the allometric scaling calculations for mice, rat and human were 0.025, 0.25 and 70 kg, respectively. Ratios of AUC at human MED to AUC at rodent ED50 were calculated. These ratios were described by summary statistics and exposure comparisons were summarised graphically.

3. Results

A total of 1274 articles were identified in the literature search across different combinations of search terms as described in the methods section. Of these, 27 articles were found to contain information on ED50 in PTZ models,[13–39] 67 in MES models,[40–106] and 27 in both models.[107–133]

Table 1 shows the mean and variability of the ED50s in mice and rat PTZ and MES models reported across the various literature papers for the nine AEDs investigated. Generally, there were fewer articles describing experiments in rats compared to mice, and more articles were found describing MES than PTZ models. ED50 values for the PTZ model ranged from approximately 10 mg/kg to 600 mg/kg across the nine AEDs investigated, and PHT and CBZ were not effective in this model. In the MES model, the ED50 values

Table 1
Average ED50 values from mice and rat PTZ and MES models across articles gathered from literature survey.

AED	Mice			Rat		
	No. of articles reporting ED50	Average ED50 (mg/kg)	CV (%)	No. of articles reporting ED50	Average ED50 (mg/kg)	CV (%)
PTZ model						
CBZ	14	NE[b]	NE	4	NE	NE
GBP	6	168	56	0	–	–
LTG	4	9.11[a]	30	1	NE	NE
OXC	2	22.8	12	0	–	–
PB	25	14.6	66	7	23.4	61
PHT	18	NE[c]	NE	9	NE	NE
TPM	4	526[a]	135	1	NE	NE
VGB	4	607[a]	3	0	–	–
VPA	37	199	76	10	551	157
MES model						
CBZ	48	11.2	44	12	9.64	108
GBP	4	105	23	1	15.0	–
LTG	22	5.26	28	3	2.80	75
OXC	13	10.8	9	0	–	–
PB	45	20.3	29	13	12.6	74
PHT	52	8.71	28	19	39.0	115
TPM	20	42.9	24	2	9.55	93
VGB	3	NE	NE	0	–	–
VPA	54	263	37	19	399	34

NE, not efficacious; CV, coefficient of variation. Some articles report ED50 values for more than one AED.
[a] 50% of articles reported AED as not efficacious.
[b] 71% of articles reported AED as not efficacious.
[c] 89% of articles reported AED as not efficacious.