The assessment of convulsion risk: a translational PK/PD modelling approach

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Introduction

Among the different central effects monitored during preclinical safety studies, convulsions are the most concerning ones.

After the preclinical characterization, the threshold to avoid convulsions in the subsequent clinical development is typically obtained dividing the no adverse event level by a factor (e.g., 10) [1].

This introduces a substantial level of subjectivity in the definition of the convulsion risk. A more thorough interpretation of the convulsion findings in preclinical experiments is recommended to define the safety margin to be applied in humans.

In particular, the risk assessment should be more appropriately based on the level of systemic exposure, rather than dose level, after having identified the most relevant pharmacokinetic metrics (e.g., Cmax) [1].

Objectives

The objective of this communication is to:
- propose a logistic model to assess the relationship between plasma concentrations and the probability of convulsions observed in preclinical studies
- predict the risk in humans.

Methods

The non-clinical convulsion data obtained in different animal species (mouse, rat and dog) for a compound under development were evaluated using nonlinear mixed effect models with the aid of NONMEM.

Models

Different logistic models were developed, exploring the potential role of compound plasma concentrations (both total and free), species and gender as predictors of the probability of convulsion.

Both linear and log-linear relationships between plasma concentrations and logits were investigated.

The different models implementing the relationships (in the linear case) are presented below.

Base Model:

```
$PRED

LOGIT = THETA(1) +THETA(2)*CONC + ETA(1)
```

Gender Model:

```
; SEX=0: Male, Reference Gender
; SEX=1: Female
$PRED

LOGIT = THETA(1) + THETA(2)*CONC + THETA(3)*SEX+ETA(1)
```

Species Model:

```
;SPEC=1: Mouse
;SPEC=2: Rat
;SPEC=3: Dog, Reference Species
$PRED
SP=0
IF (SPEC.EQ.1) SP=THETA(3)
IF (SPEC.EQ.2) SP=THETA(4)

LOGIT = THETA(1) + THETA(2)*CONC +SP+ETA(1)
```

Gender + Species Model:

```
;SPEC=1: Mouse                    ; SEX=0: Male, Reference Gender
;SPEC=2: Rat                      ; SEX=1: Female
;SPEC=3: Dog, Reference Species
$PRED
SP=0
IF (SPEC.EQ.1) SP=THETA(3)
IF (SPEC.EQ.2) SP=THETA(4)

LOGIT = THETA(1) + THETA(2)*CONC + SP+ THETA(5)*SEX+ETA(1)
```

Free Concentrations

Protein binding was concentration-dependent in all species. For this reason, non-linear models (Emax or sigmoidal-Emax) were used to fit the in vitro data. Analogous series of logistic models was developed to describe the relationship between incidence of convulsion and free plasma concentrations.

Model Evaluation

Model selection was based on statistical tests (Wald Test and Likelihood Ratio Test) and diagnostic plots such as Visual Predictive checks (VPCs) for categorical data [2].

Results

A statistically significant log-linear relationship was observed between plasma concentrations (both total or free) and the probability of convulsion. Furthermore, performing Wald Test and Likelihood Ratio Test, species was identified as a statistically significant predictor.

Table 1. Objective Function Values for different models applied on total or free plasma concentrations.

Model/ Relationship	Total plasma concentrations	Free plasma concentrations
Base/ Linear	52.669	64.08
Base/ Log-linear	45.385	56.372
Gender/ Linear	45.249	54.166
Gender/ Log-linear	39.043	48.185
Species/ Linear	42.619	47.095
Species/ Log-linear	35.418	35.698
Gender + Species/ Linear	40.884	45.066
Gender + Species/ Log-linear	34.54	34.989

The Visual Predictive Checks (VPCs) performed on the proportion of convulsions in all species showed a general good agreement between observed and simulated frequencies (Fig. 1).

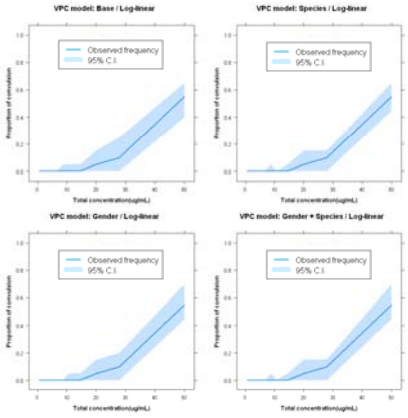

Fig.1. Visual Predictive Checks for the some of the tested models.

The log-linear models with species as covariate were selected as the final models. The corresponding parameters are listed in Table 2.

Table 2. Parameters (Standard Errors) for the final models. Species = 'Dog' is taken as the reference.

Model parameters (SE)	Total plasma concentrations	Free plasma concentrations
Intercept	-15 (3.26)	-5.64 (1.25)
Slope	3.55 (0.92)	2.84 (0.733)
Species = 'Mouse'	2.53 (1.2)	3.96 (1.26)
Species = 'Rat'	-0.337 (1.5)	-0.0596 (1.41)

The mouse species was shown to be more sensitive to convulsions (Fig 2) using both total and free concentrations [3].

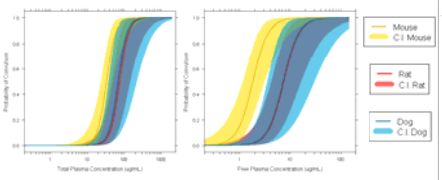

Fig.2. Estimated probabilities of the convulsive event with the corresponding confidence intervals for the different species under examination. Mixed colors derive from the superimposition of the CIs.

The assessment of convulsion risk in humans at therapeutic doses (10-40 mg) was therefore based on the most sensitive species, i.e. mouse. Both scenarios using free and total concentrations were explored (see in Table 3), and the predicted risk using the total plasma concentration resulted the most conservative approach (Fig. 3).

Tab 3. Predicted probability of convulsion at different therapeutic doses according to mouse probability model for total and free concentrations.

Doses (mg)	Cmax (5th and 95th perc.) (µg/mL)	Total concentration: Risk Probability*(%) with (95% CI)	Free concentration: Risk Probability*(%) with (95% CI)
10	0.378 (0.232 - 0.530)	4.1e-05 (2.5e-08, 0.07)	2.23e-09 (9.96e-15, 0.0005)
20	0.740 (0.464 – 1.059)	0.0005 (9.9e-07, 0.23)	1.63e-08 (1.99e-13, 0.0013)
40	1.477 (0.928 – 2.127)	0.0056 (4.03e-05, 0.78)	2e-07(8.6e-12, 0.0047)

*Predicted Probability considered at Cmax upper limit (95th perc.)

According to the model, the estimated risk of human convulsion at plasma concentrations anticipated to be of clinical benefit was < 0.01 % (95% CI < 1%).

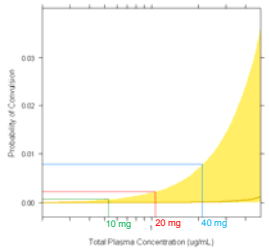

Fig 3. Predicted probability of convulsion at different therapeutic doses according to mouse probability model for total concentrations.

In our specific case, the safety margin between exposures predicted to be efficacious and exposures related to adverse event was low. In fact, considering 2 µg/mL the upper limit to be considered in clinic:
- No Adverse Event Level (6 ug/ml): 3 fold ratio
- Adverse Event Level (20 ug/ml): 10 fold ratio

Conclusions

Quantitative evaluation of convulsions in pre-clinical species can be used to predict the human risk. In addition, relevant metrics/parameters of exposure should be considered when design toxicokinetic experiments.

In our specific case, based on a traditional approach the exploration of expected therapeutic doses would have been of concern, while the objective assessment of the hazard leaded to a more robust definition of the safety margin to be applied in the subsequent clinical development.

References

[1] Cavero I. Exploratory Safety Pharmacology: a new safety paradigm to de-risk drug candidates prior to selection for regulatory science investigations. Expert Opin. Drug Saf. (2009) *8*(6):627-647

[2] M. Bergstrand, A. C. Hooker, M. O. Karlsson. Visual Predictive Checks for Censored and Categorical data, *PAGE* **18 (2009) Abstr 1604 [www.page-meeting.org/?abstract=1604]**

[3] Easter *et al*. Approaches to seizure risk assessment in preclinical drug discovery. *Drug Disc Today.* (2009) 14: 876-84