Modeling exposure-response relationships in the rat self-administration model

Andrew C. Hooker (1), Elizabeth Dunn-Sims (3), David Fairman (2), Andy Mead (3), Piet Van Der Graaf (2) and Mats O. Karlsson (1)

(1) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (2) PDM Translational Research, Pfizer, Sandwich, UK; (3) Global Safety Pharmacology Pfizer, Sandwich, UK.

Background

There is a growing emphasis on the development of methodologies to de-risk the abuse potential of drug candidates [1]. Numerous pre-clinical animal models have been proposed for investigation of the likelihood that a drug will sustain patterns of non-medical self-administration SA (abuse potential). One limitation of the current SA paradigms is that PK samples are not taken, thus they provide minimal insight into the exposure-response relationship and therefore can only be used to help define abuse potential in a qualitative manner. One proposed new SA model uses rats, with dual intravenous catheterization for infusion of drug and blood sampling, placed in a chamber with a lever that administers a possibly reinforcing test compound. Responding on the lever delivers a specific dose of the compound. The rats can then continue to respond on the lever to administer more of the compound; a specific time out between infusions limits the dosing. By varying dose per response the concentration at which reinforcing behavior occurs (if it occurs) can be determined.

Objective

To model the reinforcing behavior vs. concentration relationship and give a prediction of the dose regimen/exposure where no reinforcing behavior would be induced (with reasonable certainty) for an abused reference compound (cocaine).

Methods

Multiple study sessions with a total of 38 male Lister-Hooded rats, surgically prepared with dual catheters for simultaneous infusion of cocaine and sampling of blood were performed. Studies included:

1. A single dose PK study (no lever presses) with rich PK sampling
2. Numerous PKPD studies where dose per response was adjusted (including placebo) as well as the number of responses needed for each cocaine infusion (fig. 1).

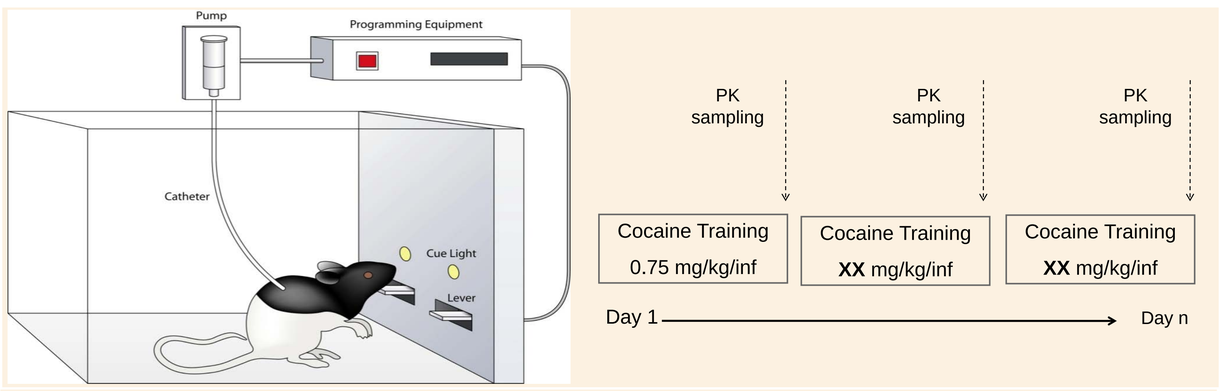

Fig. 1. Experimental PKPD setup. Rats were trained (once per day, for multiple days) to self-administer cocaine at 0.75mg/kg/infusion during a 90 minute session. Once responses were stable, a session with sparse PK sampling was performed. The same volume of heparinised saline was delivered to the animals following removal of blood to maintain homeostasis. Various dose per response levels as well as the number of responses needed for each cocaine infusion were investigated in each animal. Studies were performed with animals that had undergone repeated cocaine self-administration sessions (trained) and those in which the response had subsequently been extinguished (extinguished) via placebo (XX = 0 in figure) or very low doses of cocaine.

Results

A population PKPD model was developed sequentially (PPP&D method [2]) for this data using NONMEM (6 and 7).

PK Model: A two-compartment model with between-subject variability (BSV) on CL and V (CV of 40% and 45% respectively) and proportional residual variability (44% CV) described the PK data well (fig. 2). The data and model clearly demonstrate abuse potential resulting in a maintenance concentration of cocaine for the higher dose groups (fig. 3).

PD Placebo Model: The PD variable time-to-infusion was modeled with a repeated time-to-event model. The rats exhibited different placebo characteristics if they were trained or extinguished (exhibit fewer level presses). Thus the placebo model included terms for both states.

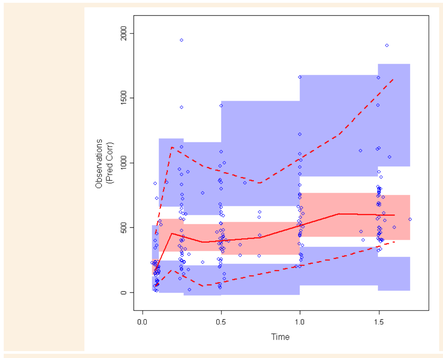

Fig. 2. pcVPC. Prediction corrected VPC of PK model fit to PK data for study type 2.

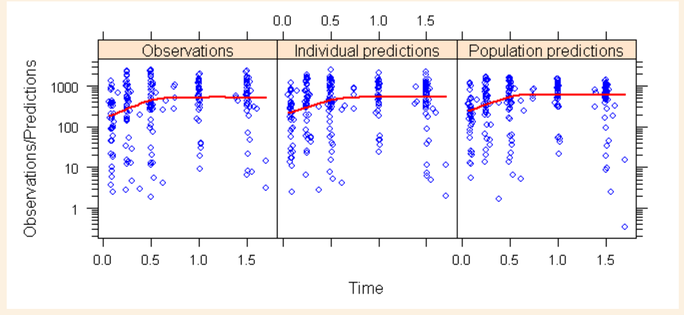

Figure 3. Observations and model predictions vs. time. PK data and model predictions for study type 2.

Placebo model for extinguished abuse potential rats (H_{p0}):

- Hazard = Weibull (experiment time) + constant
- 20 sec delay (hazard=0) after infusion
- No BSV and no covariates identified (time since last cocaine dose, time after event, Markov element, event number).

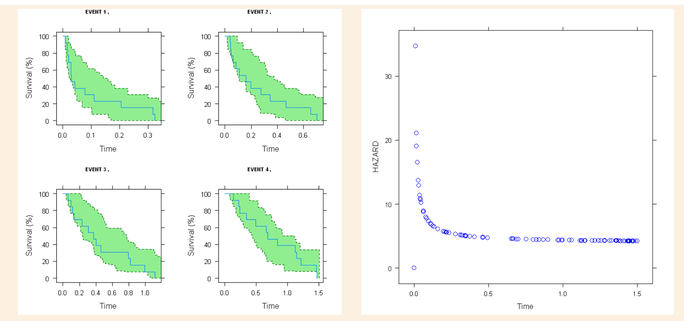

Figure 4. H_{p0} Model. Left, Kaplan Meyer VPC of first 4 events. Right, hazard function. All parameters estimated with good precision (<9% RSE).

Placebo model for trained rats (H_{p100}):

- Hazard = Weibull (experiment time)
- 20 sec delay (hazard=0) after infusion
- Exponential BSV on magnitude of Weibull
- no covariates identified

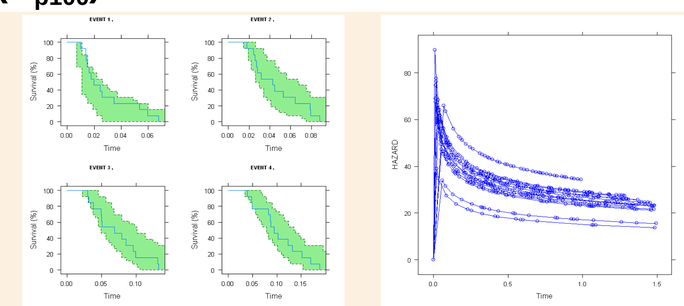

Figure 5. H_{p100} Model. Left, Kaplan Meyer VPC of first 4 events. Right, hazard function. All fixed effect parameters estimated with good precision (<11% RSE, fixed effects). 40% RSE on ω.

Drug effect

- Incorporating the PK and hazard models into a single model file was quite unstable in NONMEM. To investigate the structure of the drug effect a DOSE-response model was developed.
- Time-to-infusion (TTI) rates were 40% of H_{p100} rates (but higher than H_{p0}) for very low dose groups; at mid-dose groups TTI rates were 3-4 times higher than H_{p100} and at very high dose groups the TTI rates were again 40% of H_{p100} rates.
- Bell shaped dose effect on hazard was fit to the data
- E_{D50} estimated to 0.095 mg/kg/inf , I_{D50} estimated to 0.132 mg/kg/inf
- No BSV identified

$$Hazard = H_{p0} + (H_{p100} - H_{p0}) \cdot DR$$

$$DR = E_{\max} \cdot \left(\frac{Dose^{\gamma}}{E_{D50}{}^{\gamma} + Dose^{\gamma}} - \frac{Dose^{\gamma}}{I_{D50}{}^{\gamma} + Dose^{\gamma}} \right)$$

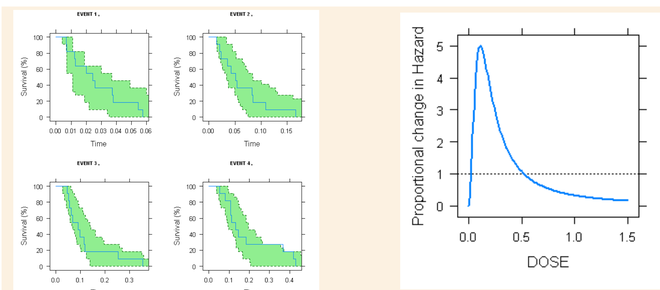

Figure 6. Drug effect model. Left, Kaplan Meyer VPC of first 4 events for DOSE=0.75 mg/kg/inf. Right, dose effect on hazard function. All parameters estimated with good precision (<12% RSE).

Conclusions

- A model that adequately describes the cocaine dose-reinforcing behavior relationship for this animal model has been developed.
- With this model as a reference, a concentration-reinforcing behavior model is being developed.
- new studies with other test compounds will be analyzed with the goal of creating a platform model to describe and predict patterns of non-medical self-administration for new compounds.
- **Future work** includes modeling time-to-lever-press, modeling acute abuse potential, and modeling of the time progression of extinction.

References

[1] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

[2] Wade and Karlsson, PAGE 1999