PKPD Modeling of Continuous and Categorical data in NONMEM

Hands-On Session – Simultaneous modeling

Combined analysis of continuous (concentration and heart rate) and time-to-event (sinus rhythm conversion) data

Introduction:

The underlying trial was a randomised, double-blind comparison of intravenously administered digoxin (n=105) and placebo (n=112) in patients with acute atrial fibrillation. The primary end point was conversion to sinus rhythm within 16 h after randomisation, while effect on heart rate was a secondary end point. Sparse (1-2 samples per subject) plasma concentration measurements were made. Heart rate (HR) was measured at 0, 2, 6, 12 and 16 hours. Of the 46% of the patients who converted to sinus rhythm the median time to conversion was 4 hours. No patient relapsed after conversion.

In the primary publication [1] of the trial, it was concluded: "The Kaplan-Meier analysis of conversion to sinus rhythm over time also showed no significant effect for digoxin (P>0.2)". A later analysis [2] reported on the population PK of digoxin and a HR model where HR was found to be dependent on TIME since start of study and digoxin concentration in effect compartment. It is now time to evaluate if any predictor of conversion to sinus rhythm (CONV) can be found using a time-to-event analysis.

The data set contains

- Dosing history
- Four types of dependent variables (identified using the FLG variable):
    - Heart rate (FLG=0)
    - Plasma concentration (FLG=1)
    - Conversion to sinus rhythm (FLG=3)
    - Censoring of time to conversion to sinus rhythm (FLG=4)
- Potential covariates
    - Treatment (TRET=1 is digoxin, TRET=0 is placebo)
    - Gender (SEX)
    - Age (AGE)
    - Weight (WT)
    - Creatinine clearance (CRCL)

Files provided:

Data sets:

dig_all1.csv	data file for PPP&D analysis
dig_all1_sim.csv	data file for simulation

Model files:
run81.mod is for PPP&D approach (Population parameters for PK and heart rate are fixed i.e. PPP&D – see lecture 1).

run81.mod = Baseline model file; only a single parameter, baseline hazard (BHAZ), is estimated.

Tasks:

1) Execute run81.mod and inspect the results, including the VPC in Figure 1.

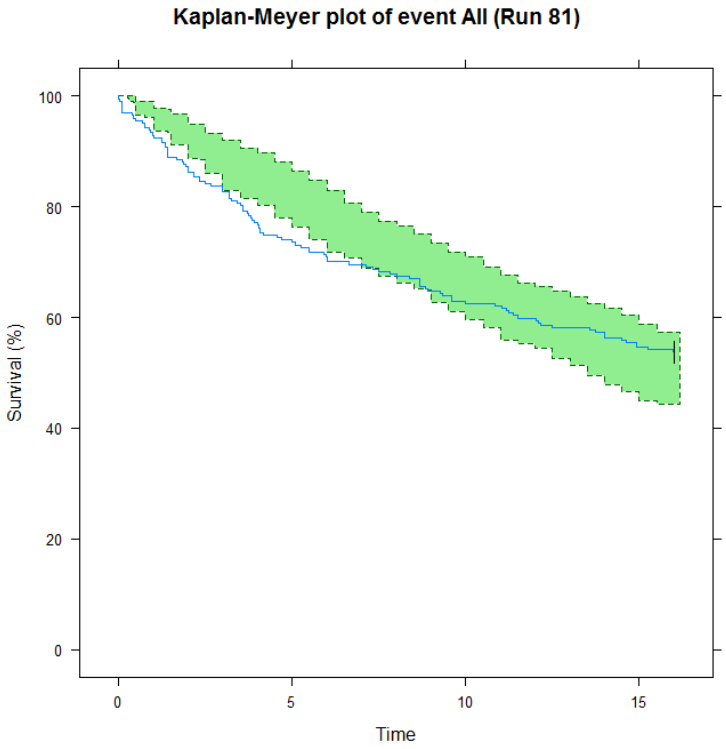

Fig 1. VPC when a constant baseline hazard was applied (run81.mod)

1) Test whether the primary result of no difference between the treatment arms is supported by your analysis, i.e. evaluate TRET as a predictive factor for conversion.

2) What other factors and variables available do you think may influence the probability for conversion? Note that many models and several parameterizations are possible.

3) Perform a VPC for your best model:
To create the necessary simulations: Run the PsN commands found in *psn_vpc_commands.txt*
To plot the results: Run the Xpose commands found in *Simultaneous_VPC.R*.

References:

[1] Hornestam B, Held P, Edvardsson N. Effects of digoxin on electrocardiogram in patients with acute atrial fibrillation--a randomized, placebo-controlled study. Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Clin Cardiol. 22(2):96-102. (1999)

[2] Hornestam B, Jerling M, Karlsson MO, Held P; DAAf Trial Group. Intravenously administered digoxin in patients with acute atrial fibrillation: a population pharmacokinetic/pharmacodynamic analysis based on the Digitalis in Acute Atrial Fibrillation trial. Eur J Clin Pharmacol. 58(11):747-55. (2003)

Table 3 Population parameter estimates for final pharmacokinetic (PK) and pharmacodynamic (PD) models

	Parameter	Unit	Typical value	RSE[a]	Between-subject variability (%)
PK model	CL[b]	l/h	9.88	0.15	66
	θ_{CrCL}[b]	min/ml	0.02	N.E.[d]	N.E.[e]
	Vc	l	27.8	0.25	N.E.
	Q	l/h	71.8	0.076	N.E.
	Vp	l	444	0.07	N.E.
	Residual error	nM	0.24	0.11	N.E.
PD model	Baseline[c]	bpm	119	0.013	17
	$\Theta_{placebo}$[c]	1/h	−0.0040	0.28	230
	$\Theta_{digoxin}$[c]	1/nM	−0.0939	0.10	N.E.
	k_{eo}	1/h	0.184	0.15	N.E.
	Residual error	%	9.0	46.6	N.E.

[a]RSE, relative standard error, is the SE divided by the parameter estimate
[b]CL for the typical patient is described by the equation: $CL = CL \times (1 + \theta_{CrCL,} \times (CrCL - 70))$
[c]HR for the typical patient is described by is described by the equation: $HR = baseline \times (1 + \theta_{placebo,} \times time) \times (1 + \theta_{digoxin} \times Ce)$, where Ce is the effect compartment concentration
[d]Not estimated. Estimate on the boundary of physiological range
[e]Not estimated. Ventricular heart rate according to ECG measurements at different time points in relation to first dose administration. Only data from patients having ongoing atrial fibrillation at each time point are included

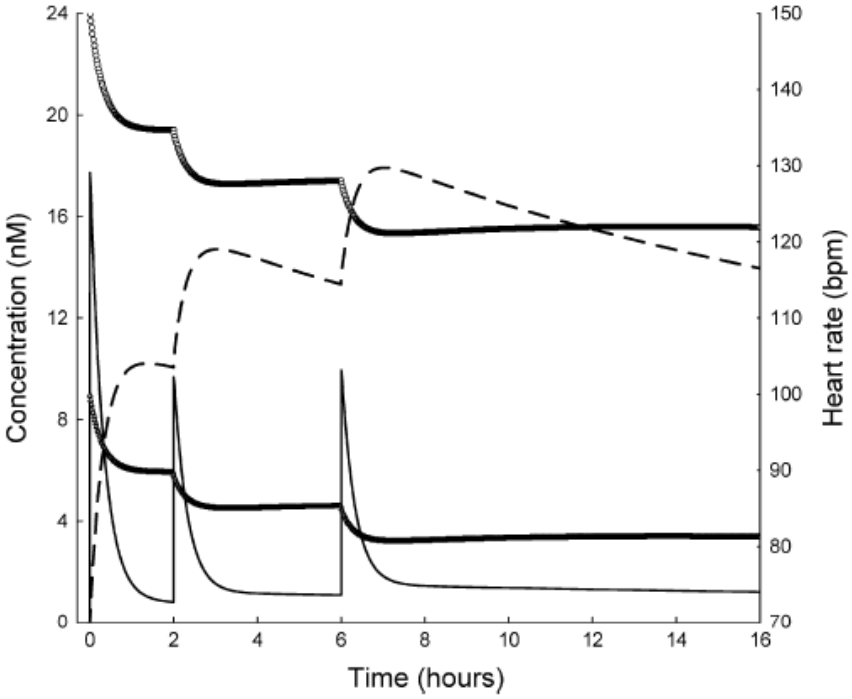

Fig. 3 Typical concentration–time profiles for digoxin in plasma (*continuous line*) and in effect compartment (*broken line*, scaled upwards with a factor of 10) with bolus doses 0.5, 0.25 and 0.25 mg given i.v. at 0, 2 and 6 h. Based on average pharmacokinetic parameters in the present study. Predicted heart rate with this regimen assuming baseline value 150 bpm (*open circles*) or 100 bpm (*open triangles*) and no conversion to sinus rhythm also shown