Pharmacokinetics / Pharmacodynamics of Intravenous Bolus Nicardipine in Adults Undergoing Cardiovascular Surgery

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Introduction

- Nicardipine is a dihydropyridine calcium channel antagonist shown to be effective in the management of hypertension with selectivity for the coronary and peripheral vasculature, and minimal negative inotropic effects.
- It is primarily metabolized in the liver via the CYP3A4 system and excreted in the bile and feces as metabolites.
- Nicardipine follows tri-exponential kinetics with a rapid early distribution phase ($t_{1/2\alpha}$ of 2.7 min), an intermediate phase ($t_{1/2\beta}$ of 44.8 min) and a slow terminal elimination phase ($t_{1/2\lambda}$ of 14.4 h).
- The pharmacokinetics of nicardipine are reported to be linear over the range of 0.5 to 4 mg/hr.
- When administered as an intravenous (IV) bolus, the antihypertensive effect of nicardipine is characterized by a rapid onset of action (~ 2 min) and a short duration of effect, making it suitable for use in perioperative conditions.
- The pharmacokinetics / pharmacodynamics (PK/PD) of nicardipine remain to be characterized in these populations.

Objectives

1. Construct a population PK / PD model to describe the effect of an IV bolus nicardipine dose on the mean arterial blood pressure in anesthetized patients undergoing cardiovascular surgery.
2. Identify covariates that are predictors of variability.

Design / Methods

- Data collected in patients undergoing cardiovascular surgery, randomized to receive one of the four doses, were used to develop the model (Table 1).
- Nicardipine was administered as an IV bolus by rapid injection (< 5s) into the right atrial port of the pulmonary artery catheter at the end of the operation if the systolic blood pressure exceeded 120 mm Hg.

Table 1: Study details and demographics

Group Dose	Group 1 0.25 mg	Group 2 0.5 mg	Group 3 1.0 mg	Group 4 2.0 mg
No. of Subjects	10	10	10	10
Age (yr)	71 ± 3	65 ± 10	71 ± 11	70 ± 12
Weight (Kg)	77 ± 12	74 ± 12	86 ± 19	81 ± 17
Sex (M/F)	8/2	8/2	9/1	7/3
General anesthetics	Midazolam, fentanyl, pancuronium, isoflurane			
PK sampling	Predose, 2, 5, 7, 10, 20, 30, 90, 120, 180, 180 and 240 minutes			
PD sampling	Systolic and diastolic blood pressure at predose, every 15s for up to 240s after nicardipine administration and every 60s thereafter for up to 30 minutes			

Model building

- The model was developed using NONMEM (version 6, Globomax, Hanover, MD).
- Exponential error model to describe intersubject variability.
- A combined additive and proportional error model was used to describe residual variability in the pharmacokinetic data while an additive error model was used to describe the residual variability in the pharmacodynamic data.

Design / Methods

Model building

- FO and FOCE with η-ε interaction .
- Model selection was guided by the goodness of fit plots, precision of the parameter estimates and changes in the intersubject and residual variability, and the objective function value.

Results

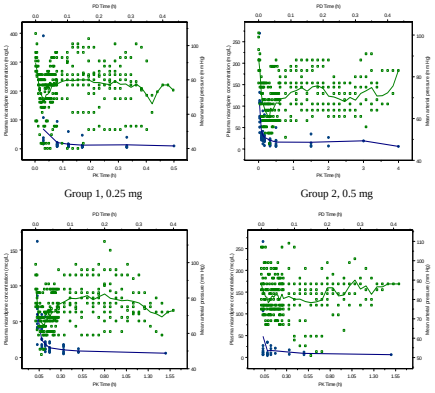

Figure 1: Plots of observed plasma nicardipine concentration (●) and mean arterial blood pressure (□) versus time. The solid line represents the mean.

Pharmacokinetic model

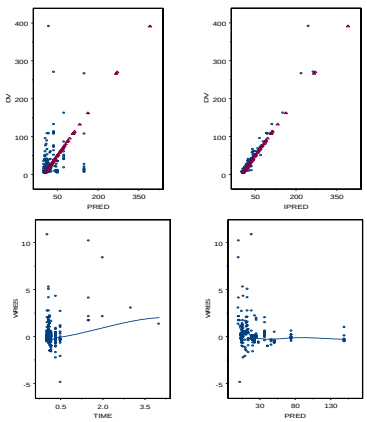

Figure 2: *Top panel:* Population (PRED) predicted, individual (IPRED) plasma concentrations *Bottom panel:* Weighted residual plots.

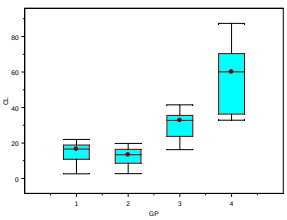

Figure 3: Plot of nicardipine clearance versus dosing groups

Pharmacokinetic/Pharmacodynamic Model

Table 2: PD model building

Model	Feature	Comment
Inhibitory Emax	Direct relationship between plasma level and effect Most parsimonious	FO OFV = 8666 Extremely poor fits Numerically unstable with FOCEI
Indirect response	Effect-time profile lags behind the concentration-time profile	FO OFV = 8318 Fails to describe the drop in MAP Numerically unstable with FOCEI
Indirect response – modulator (PD Tolerance)	Inherent counter-regulatory mechanism	FO OFV = 7445 Good description of MAP FOCEI OFV=7266 Good description of MAP

Results

Pharmacokinetic/Pharmacodynamic model

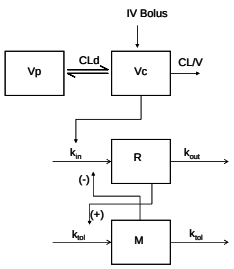

Figure 4: A schematic of the current PK/PD model

Table 3: Parameter estimates of the current PK/PD model

Parameter (units)	Mean value (%CV)	% IIV (%CV)
CL (L/hr)	43.5 (33.1)	136 (28.9)
V1 (L)	1.18 (51.4)	196 (31.34)
Q (L/hr)	17.5 (37.2)	-
V2 (L)	4.44 (17.3)	-
Kin (mmHg/h)	3170 (12.6)	10.3 (44)
Kout (h^{-1})	36 (12.6)	8.6 (60.7)
Emax	1 (fixed)	-
EC50 (mcg/mL)	361 (22.9)	123 (38.4)
Ktol (h^{-1})	0.00373 (29.7)	144 (40)
Residual error PK - σ_{ppn} PK - σ_{add} (µg/L) PD - σ_{add} (mm Hg)	 30% (21.6) 2.2 (26.8) 18.8 (12.8)	

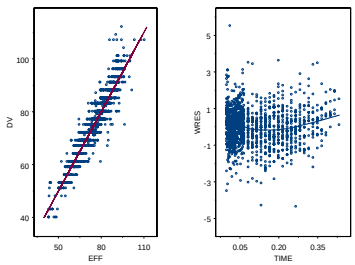

Figure 5: Plot of predicted (EFF) and observed MAP (DV) and weighted residuals (WRES) versus time for the current PK/PD model.

Discussion / Conclusions

- A graded increase in clearance was observed with increasing doses.
- None of the patient characteristics/covariates tested explained the observed increase in clearance.
- Increasing doses of nicardipine result in greater magnitude and duration of vasodilation, which may lead to an increase in its clearance (distributional / elimination).
- The current model incorporates the inherent counter-regulatory mechanism (mediated by baroreceptors) involved in blood pressure control.
- Concentration-time and MAP-time data obtained from this study was not optimally sampled, therefore making characterization of the clinically effective half-life difficult.
- Several patients in groups 3/4 received phenylephrine to reverse severe hypotension and the observed decrease in MAP is a result of the opposing effect of the two agents.
- The existing single dose data alone is not sufficient to derive dosing guidelines in this population. Results of this data analysis will however contribute significantly to the design of a prospective study in this population.