

POPULATION PK/PD MODELING OF SUPINE HEART RATE AFTER ORAL ADMINISTRATION OF A NEW CANDIDATE ANTIPSYCHOTIC DRUG



An Vermeulen, PhD and Filip De Ridder, PhD
Johnson & Johnson Pharmaceutical R&D, Beerse, Belgium

INTRODUCTION

A new stereochemically pure chemical compound showing central D₂ combined with predominant 5HT_{2A} antagonism has been synthesized. In addition to putative antipsychotic effects, the compound is effective in animal models of anxiety and depression and seems to stimulate social behaviour. This is thought to be due to its ability to block central 5HT_{2C} receptors and to inhibit norepinephrine re-uptake.

In the first clinical studies, the compound increased heart rate, especially in the supine position, which is thought to be related to its noradrenaline reuptake inhibiting properties. In order to help with the selection of doses that could be safely administered in subsequent clinical trials, a population PK/PD analysis was undertaken.

OBJECTIVES

The main objectives of the current analysis were :

- ✓ to model the supine heart rate (HR, calculated from the RR interval of the ECG, according to $HR=60000/RR$) after oral administration of a solution (0.5-88 mg) or a capsule (5-75 mg) formulation;
- ✓ to get estimates of typical pharmacodynamic parameters in the healthy and patient population and of their inter- and intraindividual variability;
- ✓ to evaluate the effects of patients' demographic characteristics and other covariates on the compound's pharmacodynamics;
- ✓ to perform simulations to better understand the dose-response relationship and help in the selection of doses for subsequent trials.

METHODS and RESULTS

✓ The NONMEM V level 1.1 software program (GloboMax, Hanover, MD, USA) was used for all model fittings. The package was installed on a PC platform using Microsoft Powerstation 4.0 under Microsoft Windows 2000. The first-order (FO) approximation method was used throughout the analysis.

✓ Data both from phase 1 and phase 2 trials were used, and model-predicted concentrations at the time of the (supine) ECG measurements were used as drivers of the response. The database consisted of 777 subjects, and 8172 observations. In total, 669 patients and 108 healthy subjects were included in the analysis.

✓ The population PK/PD model was built assuming that there was a direct relationship between plasma concentrations and supine HR (no delay) and that no tolerance over time develops.

The final model is of the form: $HR = BSL * (1 + DIUR + DEFF)$,

where HR stands for supine heart rate, BSL for baseline heart rate, DIUR for the diurnal rhythm component (sum of 2 cosine functions) and DEFF for the drug effect.

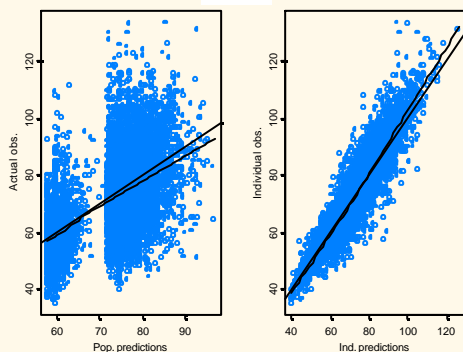
The drug effect is described as follows:

$$DEFF = EMAX * (CP^{HILL}) / (EC50^{HILL} + CP^{HILL}),$$

where EMAX is the maximum proportional increase in heart rate with respect to baseline, CP is the model-predicted plasma concentration at the time of the ECG measurement, EC50 is the concentration at which the half-maximum effect is reached and HILL is the Hill factor.

The IIV was additive for BSL and all parameters related to the rhythm, and proportional for all parameters related to the drug effect. The IOV in BSL was also additive.

Only demographic variables, study and genotype information were included in the covariate analysis, since lab parameters were not available for all trials at the time of the analysis. Finally, correlation testing was performed.



Plots of Measured Heart Rate Against Posterior Population (Left Panel) and Individual (Right Panel) Predictions (Circles) (Final Run). Full Lines are Identity Lines, and Local Smoothers

CONCLUSION: Predictions using the final population PK/PD model show that up to doses of 35-40 mg, less than half of the patients have increases in supine HR of 6 beats/min at peak. This range increases to 55-60 mg if average instead of peak steady-state concentrations are considered. Therefore, safety problems are to be anticipated only when doses higher than 40 mg/day are administered.

Results expressed as parameter with the relative standard error (%) in brackets

Parameter	Central tendency	IIV*	IOV*
BSL, beats/min		SD 7.90 (8.43)	SD 3.24 (13.2)
Healthy volunteers, M+F	51.9 (2.45)		
Patients, M	64.7 (2.24)		
Patients, F	68.8 (2.27)		
AMPI	-0.234 (14.3)	SD 0.026 (225)	-
PH1, h	17 (1.44)	SD 1.71 (25.2)	-
AMP2	-0.119 (10.2)	SD 0.031 (40.1)	-
PH2, h	4.69 (3.99)	SD 1.51 (34.2)	-
EMAX, %	43.7 (31.1)	60 (24.6)	-
EC50, ng/mL	35.1 (63.3)	0, FIX	-
HILL	0.762 (12.8)	49 (80.0)	-
Residual variability			
phase 1 trials	SD 5.94 (6.60)		
phase 2 trials	SD 9.15 (7.68)		

* IIV and IOV are presented as %CV, unless indicated otherwise (SD)

The model predicts that BSL is different between healthy volunteers, irrespective of sex, and patients, and within the patient group, between males and females. The low BSL HR in healthy volunteers is probably related to the fact that most of them were males with an excellent physical condition. The heart rate was found to show diurnal rhythm during the day, and this rhythm was best described by the sum of 2 cosine functions.

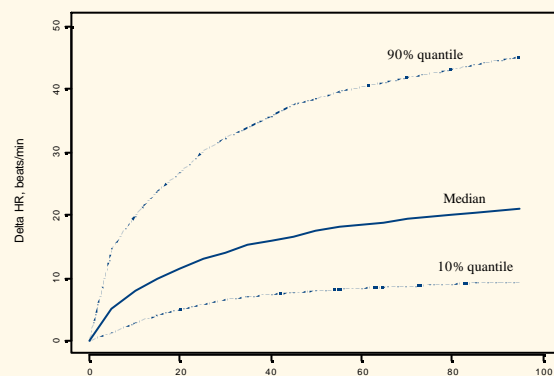
The drug effect model was best represented by a sigmoidal E_{max} function. The relationship between plasma concentrations and supine HR was shallow (Hill factor of 0.762).

No IIV in EC₅₀ could be estimated from the data, whereas for E_{max} and Hill, IIVs of 60 and 49 % were observed. All other parameters (BSL and diurnal rhythm related) show variabilities of around 30% or lower. Interoccasion variability was implemented for BSL HR, and was lower than 10%.

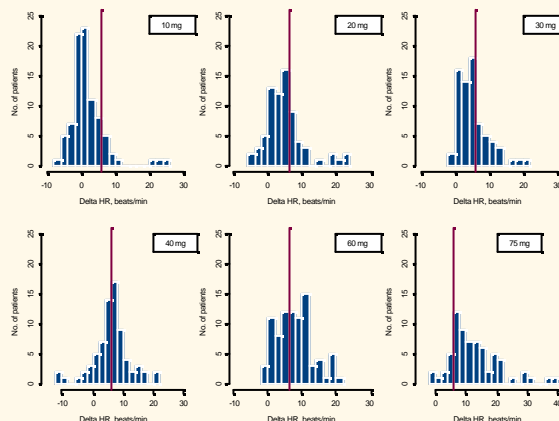
The correlation between PH1 - PH2 amounted to 0.91, with relative standard error of 33%.

The relative standard error of all structural parameters was below 50%, with the exception of the EC₅₀.

It was below 50% as well for most variability parameters, with notable exceptions for the Hill factor and AMP1, indicative of a relatively poor estimation of these parameters.



Increase in Supine HR versus Plasma Concentration, as Predicted by the Final Population PK/PD Model. The Quantiles Reflect the Interindividual Variability.



Histograms Showing the Distribution of the Individual Predictions of the Change in HR for the Patients Included in the Phase 2 trials. The Vertical Red Line Shows an Increase of 6 beats/min.