DEVELOPMENT OF A JOINT DISSOLUTION AND PHARMACOKINETIC MODEL OF PROPAFENONE AND ITS HYDROXYLATED METABOLITE

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Introduction

Propafenone (PRO) is a class 1C antiarrhythmic agent, indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients with episodic atrial fibrillation who do not have structural heart disease. PRO undergoes extensive and saturable first-pass metabolism, resulting in a dose and dosage form dependent absolute bioavailability (3.4% and 10.6% for a 150 mg and 300 mg immediate release (IR) tablets, and 21.4% for a 300 mg solution). The relative bioavailability of the sustained release (SR) dosage form is lower than the IR formulation, as the more gradual release of PRO from the SR preparation results in an increase of overall first-pass metabolism.

Two genetically determined patterns of PRO metabolism are found in the population. The drug is rapidly and extensively metabolized with an elimination half-life ($t_{½}$) from 2 to 10 h in over 90% of patients (extensive metabolizers). These patients metabolize PRO into two active metabolites: 5-hydroxypropafenone (5-OHP) which is formed by CYP2D6 and N-depropylpropafenone, which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients (defined as poor metabolizers), metabolism of PRO is slower because the 5-OHP metabolite is not formed or is minimally formed, resulting in higher PRO plasma concentrations and prolonged elimination $t_{1/2}$ (from 10 to 32 h) [1-4]. Poor metabolisers are identified through the diminished ability to metabolize debrisoquine.

Objectives

The aim of the present study was to investigate PRO and 5-OHP pharmacokinetics (PK) following oral administration of SR PRO, through the development of a joint PK model able to characterize the dissolution, absorption and disposition kinetic processes.

Methods

- ***In Vitro* Data:** Dissolution was performed using a two stage method (2h at HCl 0.1N followed by pH 6.8 phosphate buffer), USP apparatus II (Paddle), 50 rpm, n=12.
- ***In Vivo* Data:** A total of 88 plasma concentration-time profiles of PRO and 5-OHP were obtained from 65 healthy subjects (27 males [41.5%] and 38 females [58.5%]; with 60 subjects being extensive metabolizers [92.3%] and 5 poor metabolizers [7.7%]) included in two bioequivalence studies conducted under fed conditions (high fat high calorie) with 425 mg PRO SR capsules.
- **Pharmacokinetic Modelling:** A joint parent-metabolite PK structural model was implemented in Phoenix NLME version 8.3 The model included the mean *in vitro* dissolution data to correlate with *in vivo* PRO dissolution for a better prediction of the absorption kinetics of the drug.
- **Model Evaluation:** Prediction errors of the PK metrics (C_{max} and AUC), as well as goodness of fit plots and normalized prediction distribution error method were used for model validation.

Conclusions

The mean prediction error of the model was less than 2% for PRO and 5-OHP AUC, and was moderately high for C_{max} (19% for PRO and 17% for 5-OHP). Nevertheless, the developed structural joint model adequately described plasma concentration-time profiles for PRO and 5-OHP in healthy subjects.

Table 3. Prediction errors of the PK metrics (C_{max} and AUC)

PRO (n=88)			5-OHP (n=88)		
C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
19.14	-1.82	-2.20	17.19	1.89	0.35

References

[1] U.S. Food and Drug Administration (FDA). RYTHMOL SR (propafenone hydrochloride extended-release capsules), for oral use. Revised Version: February 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021416s015lbl.pdf.

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Results

In Vitro Dissolution Data

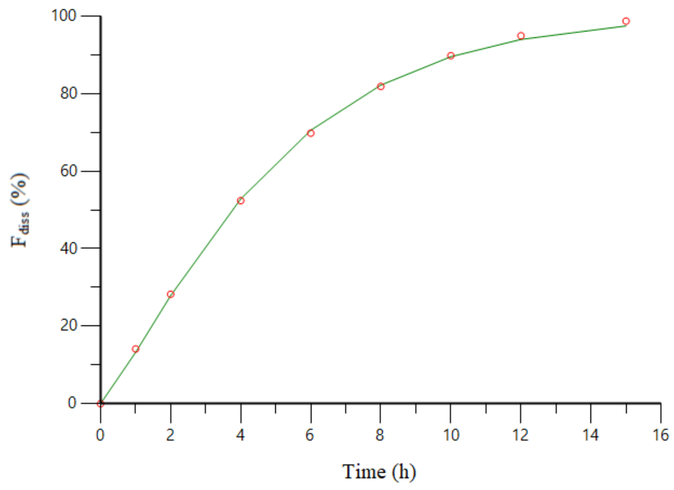

Figure 1. *In vitro* dissolution data (dots) fitted to a Weibull model (line)

Weibull Model Equation:

$$F_{diss} = F_{max} \cdot \left(1 - e^{-t^{\beta}/\alpha}\right)$$

Table 1. Weibull Dissolution Model Parameters

F_{max} (%)	α	β
100	7.03	1.20

In Vivo Parent and Metabolite Plasma Concentration Data

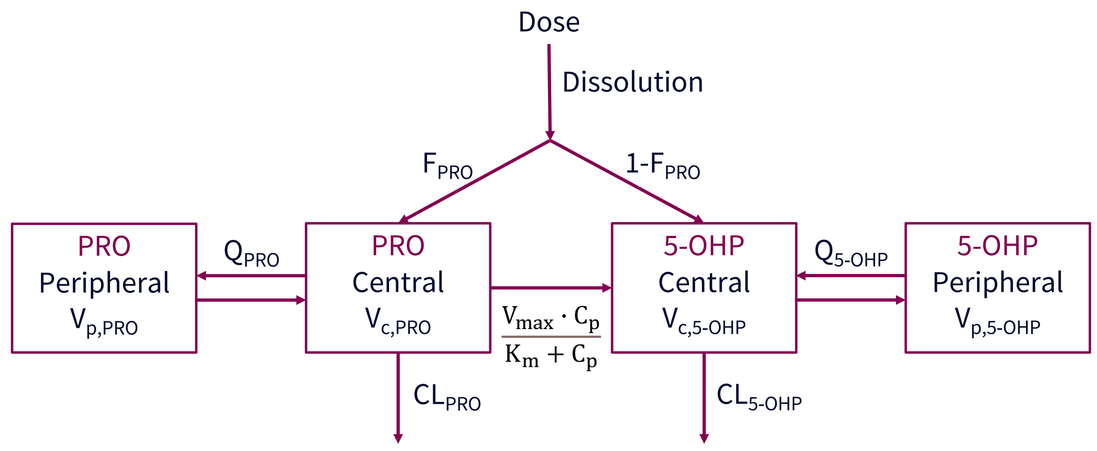

Figure 2. Schematic representation of final parent-metabolite joint structural pharmacokinetic model, for PRO and 5-OHP. *F_{PRO} fraction of parent (PRO) reaching systemic circulation after dissolution and absorption, $V_{c,PRO}$ volume of distribution of Propafenone for the central compartment, $V_{c,5-OHP}$ volume of distribution of metabolite 5-OHP for the central compartment, CL_{PRO} clearance of Propafenone by other processes than the metabolic conversion to 5-OHP, CL_{5-OHP} clearance of metabolite 5-OHP, Km Michaelis-Menten constant for the metabolic conversion of Propafenone into 5-OHP, V_{max} theoretical maximum rate for the metabolic conversion of Propafenone into 5-OHP, Q_{PRO} intercompartmental clearance for Propafenone, Q_{5-OHP} intercompartmental clearance for metabolite 5-OHP.*

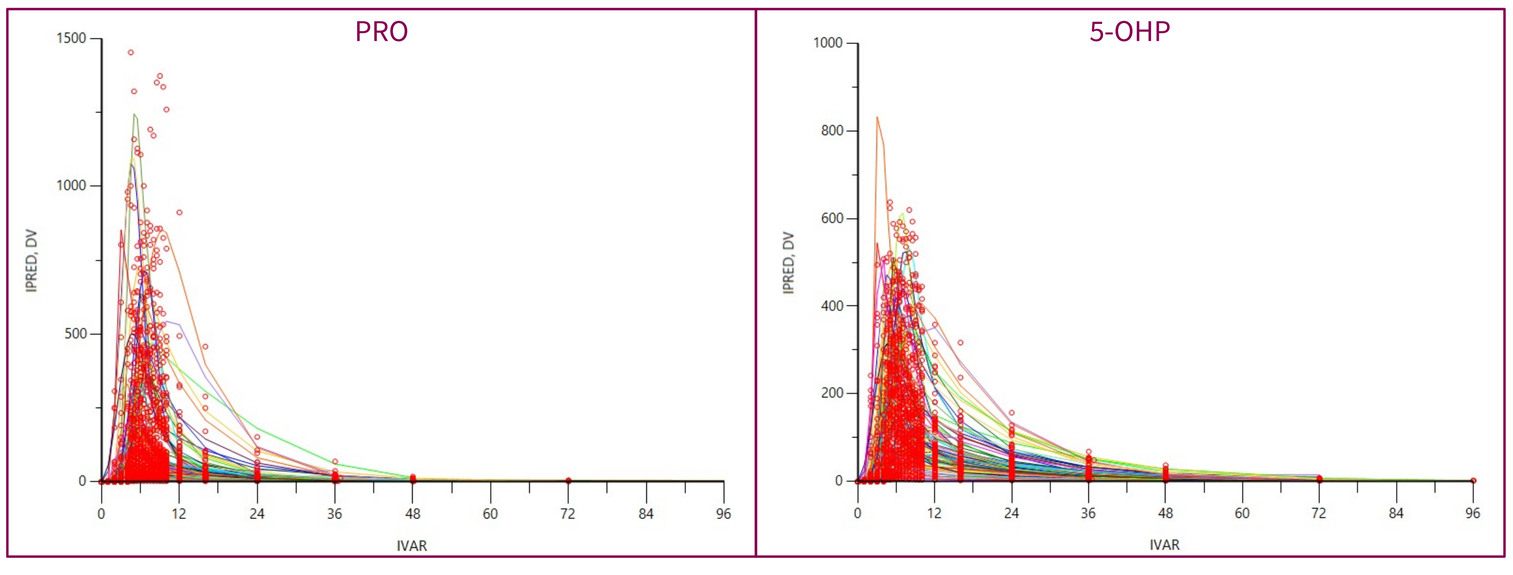

Figure 3. Observed (dots) and predicted (lines) plasma concentration-time profiles, of PRO and 5-OHP

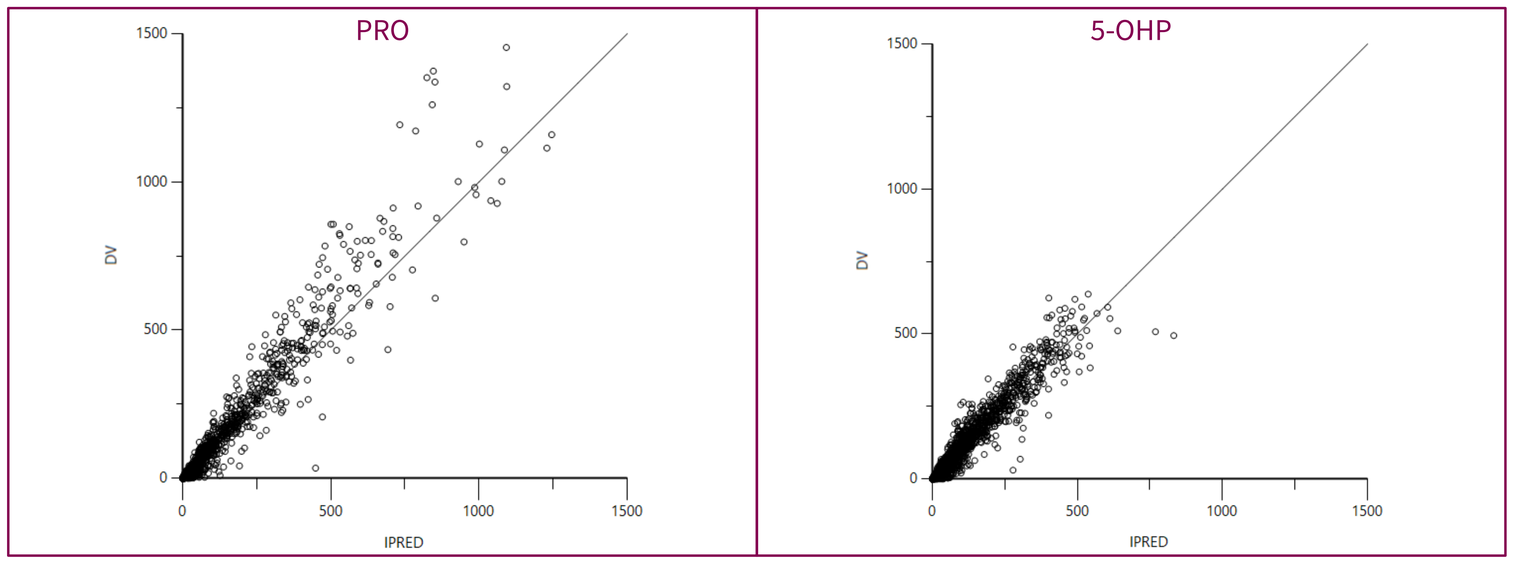

Figure 4. Goodness of ft plots for PRO and 5-OHP

Table 2. Geometric mean of the estimated individual PK parameters

F_{PRO}	Scale α	Scale β	$V_{c,PRO}$ (L)	CL_{PRO} (L/h)	$V_{p,PRO}$ (L)	Q_{PRO} (L/h)	K_m (nmol/L)	V_{max} (nmol/h)	$V_{c,5-OHP}$ (L)	CL_{5-OHP} (L/h)	$V_{p,5-OHP}$ (L)	Q_{5-OHP} (L/h)
0.037	3377	3.90	30.25	1.02	122.0	17.17	32.33	240.2	104.1	305.4	1887.4	538.5

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