Population Pharmacokinetic Simulations of Two Paliperidone Palmitate Formulations

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OBJECTIVES

To investigate dosing strategies for paliperidone palmitate 3-month formulation (PP3M), to explore the impact of selected covariates using the developed population paliperidone palmitate pharmacokinetic (PK) models, and to derive secondary PK parameters from the model.

BACKGROUND

Paliperidone is the major active metabolite of risperidone and is used in the treatment of schizophrenia. Two formulations of paliperidone are currently available: an extended-release (ER) paliperidone formulation for daily (QD) oral administration, and a long-acting injectable paliperidone palmitate 1-month formulation (PP1M) for monthly intramuscular administration. A modified paliperidone palmitate formulation is currently under development, which potentially can be administered every 3 months with retained efficacy.

METHODS

A 1-compartment model with parallel zero and first-order absorption describing the PK of PP1M [1] and a 1-compartment model with 2 saturable absorption processes describing the PK of PP3M [2] were used for simulations in R. Covariates were obtained by resampling subject covariates in the PK database for PP1M and PP3M. Simulation scenarios with varying doses and covariate values were generated. The population median and 90% prediction interval (PI) of the simulated concentration-time profiles were plotted for simulation outcomes evaluation.

CONCLUSION

The explored PK simulation scenarios provided important guidance on PP3M dosing in schizophrenic patients and supported a once every 3 months injection cycle.

RESULTS & DISCUSSION

Figure 1 shows that paliperidone's PK, when administered as PP3M, was not significantly altered in subjects of different sex, using the deltoid or the gluteal injection site, or the needle lengths. Moreover, the trough paliperidone plasma concentrations were similar in subjects with different BMI, once stabilized on treatment with PP3M. However, female sex, higher BMI (overweight or obese subjects), and using the gluteal site of injection delays the time to achieve therapeutic concentrations if subjects are not correctly initiated with PP1M before transitioning over to PP3M.

Weight based needle lengths for deltoid injections were used in the PP3M studies and switching to PP3M was always preceded by deltoid based PP1M initiation and PP1M stabilization. Neither BMI nor needle length were found to be significant covariates in the PP3M population PK model. Therefore, it may be inferred that a longer injection needle in the deltoid muscle mitigates some of the BMI effect on PP3M absorption. Thus, after multiple injections of PP3M, paliperidone trough concentrations were similar for PP3M in normal, overweight, and obese patients with schizophrenia in the population-PK simulations.

Age was not a statistically significant covariate in the final population PK model. The same paliperidone exposure is therefore expected in elderly and young subjects when differences in CRCL between age groups have been accounted for. BMI varies by race and once the impact of BMI is incorporated in the model, race does not influence PP3M PK. Liver function tests were not identified as statistically significant covariates on the clearance parameter in the population PK model for PP3M.

A dose of 525 mg eq.** of PP3M in subjects with mild renal impairment produced simulated exposures higher than those achieved with the highest studied dose of 525 mg eq. in subjects with normal renal function. Dose adjustment for renal impairment is done when initiating PP1M treatment (25% dose reduction), and then subjects can be transitioned over to the corresponding 3.5 multiple PP3M dose for mild renally impaired subjects. No additional dose reduction upon starting PP3M is necessary. One subject with moderate renal impairment and no subjects with severe renal impairment were included in the analysis and the model cannot be used to predict paliperidone's exposure in these sub-populations.

The derived secondary PK parameters are presented in Table 1. Peak plasma concentrations for a typical patient were achieved within 30-33 days after a single PP3M injection over the dose range of 175-525 mg eq. The PK of paliperidone palmitate was dose-proportional for overall exposure over the dose range of 175-525 mg eq. and appeared to be dose-proportional for maximum concentration. At steady-state, the PP3M peak-to-trough ratio was 1.6-1.7 following gluteal and deltoid administrations, which is similar to the peak-to-trough ratios following deltoid PP1M injections. The apparent half-life of the PP3M formulation was in the range of 84-95 days following a deltoid injection and 118-139 days following a gluteal injection.

Table 1. Derived secondary PK parameters

Repeated dosing

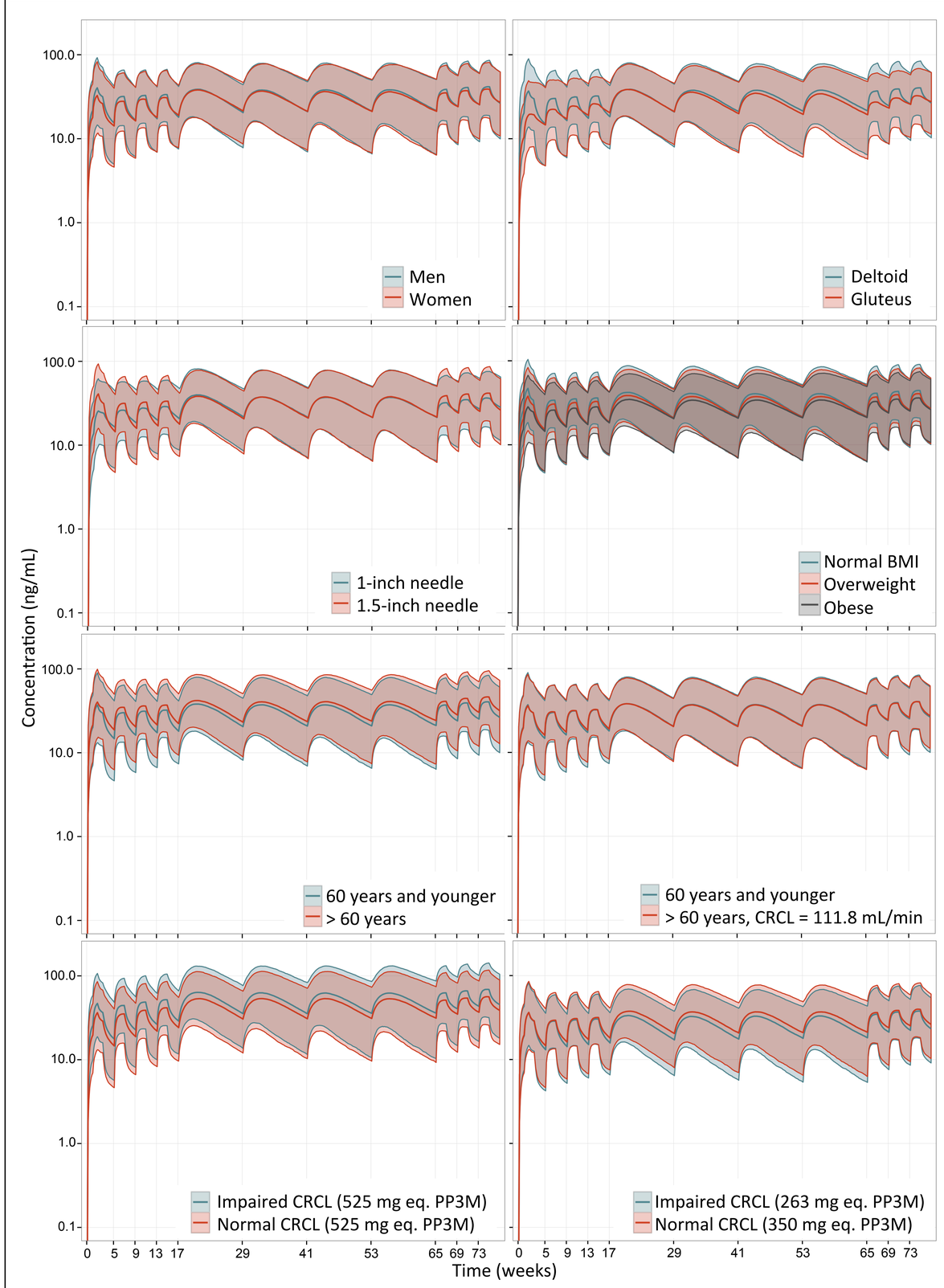
	PP3M				PP1M		
Injection site	**Dose (mg eq.)**	**C_{max} (ng/mL)**	**C_{max}/ Dose**	**Peak/ Trough**	**Dose (mg eq.)**	**C_{max} (ng/mL)**	**Peak/ Trough**
Deltoid	175	20.8	0.12	1.7	50	19.9	1.8
	263	30.2	0.11	1.7	75	27.7	1.7
	350	39.1	0.11	1.7	100	35.3	1.7
	525	56.4	0.11	1.6	150	49.9	1.6
Gluteal	175	18.8	0.11	1.7	50	16.7	1.3
	263	27.2	0.10	1.7	75	23.4	1.3
	350	35.2	0.10	1.7	100	29.6	1.3
	525	50.9	0.10	1.7	150	41.4	1.2

Single dose

Injection site	**Dose (mg eq.)**	**T_{max} (days)**	**$t_{1/2}$[a] (days)**	**C_{max} (ng/mL)**	**C_{max}/dose**
Deltoid	175	30	83.5	14.5	0.08
	263	31	87.1	21.2	0.08
	350	32	90.2	27.6	0.08
	525	33	94.9	40.2	0.08
Gluteal	175	30	117.8	12.9	0.07
	263	31	124.9	18.9	0.07
	350	32	129.5	24.7	0.07
	525	33	138.5	36.0	0.07

a The apparent half-life was not constant over time (multi-exponential profile) due to the saturable component of the absorption sub-model. Therefore, the maximal apparent half-life was derived during the second part of the multi-exponential profile reflecting the terminal decline phase (about 25 weeks after the first injection)

Figure 1. Simulated paliperidone plasma concentrations versus time



The solid lines and shaded areas represent the median paliperidone concentrations and 90% PI.

Table 2. Paliperidone doses used in the simulations

Formulation[a]	PP1M	PP1M	PP3M
Dose time point	Day 1	Day 8, Weeks 5, 9, 13, 65, 69, 73	Weeks 17, 29, 41, 53
Dose	150 mg eq.	100 mg eq.	350 mg eq.

[a] Unless stated otherwise, deltoid paliperidone palmitate injections were used in the simulations

[1] Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: a novel once-monthly, long-acting formulation of an atypical antipsychotic. Clin Pharmacokinet. 2009;48(9):585-600

[2] Magnusson MO, Samtani MN, Plan EL, Jonsson EN, Rossenu S, Vermeulen A; Population Pharmacokinetic Modeling of Paliperidone Palmitate 3-Month Formulation. PAGE (2015)

**All paliperidone palmitate quantities are expressed as mg eq. of paliperidone

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