A semi-mechanistic model to characterize the pharmacokinetics of orally administered *S*-Ketamine in healthy human subjects

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Background and Goal:

Low-dose *S*-ketamine has been documented to provide adequate level of analgesia, however optimal dosing regimen for it's use in pain medicine still remains to be established. We developed a semi-mechanistic population model to characterize the highly variable pharmacokinetic (PK) profile of orally administered *S*-ketamine in healthy human volunteers.

Materials and Methods:

- Concentration-time and covariate data (age, weight and gender) from five previously conducted placebo-controlled, blinded, randomized, crossover studies[1-5]
- 56 healthy volunteers, 28 females, 28 males (age 19 - 31 years and body weight 49 - 92 kg)
- Single dose of oral (0.2 or 0.3 mg/kg) or intravenous (0.1 mg/kg) *S*-ketamine
- Total of 15 venous blood samples at predefined time intervals during 24 hours
- Drug concentrations were analysed with validated HPLC-MS/MS method[2]
- Non-linear Mixed Effects Modelling with NONMEM 7.3.0 software (ICON Development Solutions, Dublin, Ireland). Perl modules implemented in Perl-Speaks-NONMEM (PsN) and R based scripts were used to coordinate model runs and for model diagnostics

Final model

- Single **Weibull absorption** function for oral *S*-ketamine absorption
- **Well stirred clearance** model for *S*-ketamine gut-wall and hepatic first pass metabolism
- **Three compartmental catenary model** for *S*-ketamine disposition kinetics
- **Physiological recirculation** of the drug from central compartment through portal vein and hepatic artery into the liver compartment
- Gut-wall and hepatic extraction of *S*-ketamine as input for the norketamine model
- **Two compartmental mammillary** model for norketamine disposition kinetics
- **Well stirred clearance model** implemented in gut-wall and liver compartments for first pass, as well as **physiologically recirculated** norketamine elimination

Results

- Diagnostic plots and prediction corrected visual predictive checks indicated, that a catenary ketamine model resulted in a good fit and plausible parameter estimates, contrary to a mammillary model, which could not provide quantitative measures of compartment volumes. (Fig.1 and Table 1)
- Ketamine is a highly lipophilic drug with a large V_D, and the model results suggest a small central compartment volume as opposed to the volumes of peripheral compartments (Table 1)
- Plausible values for central volume could only be obtained after addition of IV data to the model
- The ratio of model predicted hepatic to gut-wall *S*-Ketamine clearance is 1:85 (Table 1)
- Norketamine kinetic profile was adequately accounted for by a semi-mechanistic model with first pass and circulatory clearance from the gut-wall and liver sites of elimination

Conclusion

The semi-mechanistic non-linear mixed effects modelling approach used in this study adequately described the pharmacokinetic profile of *S*-Ketamine and its primary metabolite Norketamine.

References

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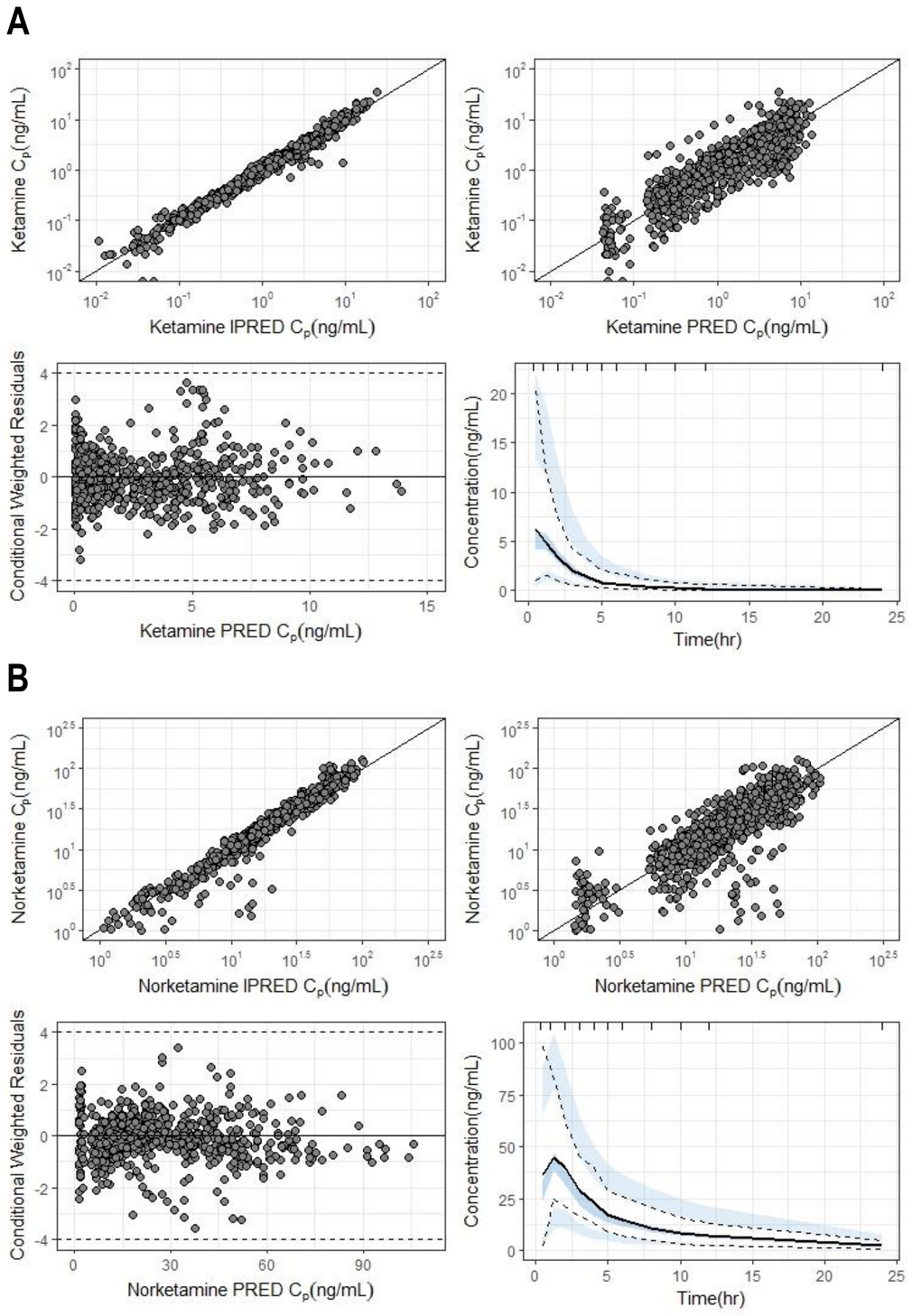
Table 1. Parameter estimates from final semi-mechanistic model

Parameter	Value (%RSE)	IIV% (%RSE)
S-KETAMINE		
V1 (L)	2.3 (16)	-
Q (L/hr)	39.2 (11.5)	-
V2 (L)	63.6 (8.4)	-
Q2 (L/hr)	9.8 (13.1)	-
V3 (L)	57.9 (11.7)	-
KA (1/hr)	2.6 (23)	74.8 (19)
Shape factor (SF)	1.96 (3.7)	-
CLH (L/hr)	114.2 (15.7)	34.5 (26.2)
CLG (L/hr)	1.34 (24.8)	57.7 (15)
NORKETAMINE		
V4 (L)	35.6 (5.8)	-
Q3 (L/hr)	49.8 (5.6)	-
V5 (L)	137.2 (3.3)	-
CLHM (L/hr)	82.4 (10)	35.2 (21.1)
CLGM (L/hr)	0.02 (67.2)	154.8 (41.3)

Figure 1. Diagnostic plots for *S*-ketamine (A) and Norketamine (B)



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