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A joint ketamine and esketamine exposure-response model of MADRS score in major depressive disorder to enable informed trial design for candidate drugs with similar mode of action

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Objectives

This work aimed to develop a pharmacokinetic-pharmacodynamic (PKPD) model based on digitized MADRS score data and to perform simulations to demonstrate the utility of the model for dosage optimization of ketamine, and drugs with similar mode of action.

Background

- Ketamine and esketamine have been shown to have positive effects on Montgomery-Åsberg Depression Rating Scale (MADRS), an endpoint commonly utilized to measure drug effects in major depressive disorder (MDD).
- Twice and thrice weekly (2W/3W) administration of ketamine (0.5 mg/kg IV, ~4 weeks of treatment plus >2 weeks of follow up, n=18 and n=16 respectively)[1], and 3W dosing of esketamine (0.2, 0.4 mg/kg IV, 7 days, n=9 and n=11 respectively)[2] has been studied. In the same trials, placebo was also studied given 2W or 3W.

Methods

Individual MADRS scores (treated as continuous) were digitized using WebPlotDigitizer[3]. A population PKPD model built on a ketamine dose titration study, with wash out between dose escalations[4], was evaluated but could not describe the combination of short and long-term (4 weeks) data including follow-up. No PK data was included in the analysis.

An indirect response model with positive feedback, suitable for long lasting effects after short treatment interventions with slow return to baseline, was tested[5]. The drug effects tested, stimulating the feedback rate, were linear and Emax models.

The model was extended with a proportional placebo component implemented on the positive feedback compartment at baseline. A tolerance model and differences in potency between ketamine and esketamine were tested.

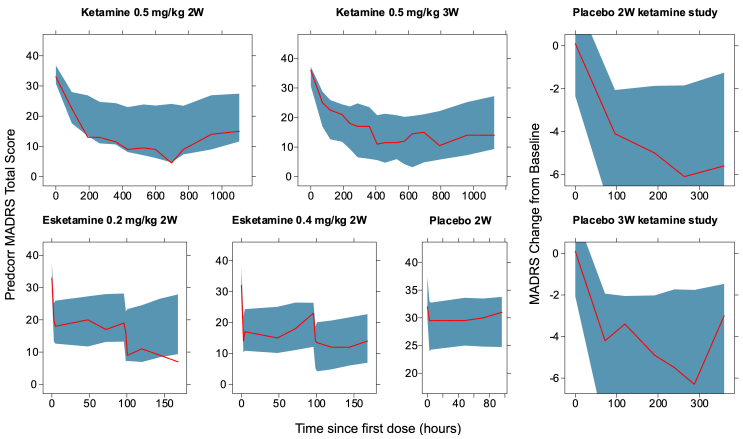

Figure 1. *Prediction corrected visual predictive checks per arm based on 300 simulated datasets. The lines are the median of observed data and shaded areas are 95% confidence intervals for the median based on simulated data.*

Based on the model, MADRS scores over 6 weeks were simulated after 0.125, 0.5 and 2 mg/kg ketamine as I. a single dose, II. 4 weeks of dosing every fourth day, and III. 6 weeks of dosing with the same frequency. Subsequently, a 2 mg/kg/week dosing was simulated given once daily, every fourth day or once weekly.

Conclusions

- The model described the ketamine, esketamine and placebo data well and can be used as a framework to inform design of trials for ketamine/esketamine or drugs with similar mode of action.
- The simulations suggested that treatment of MDD may benefit from a loading dose followed by daily maintenance dosing.

Results

- The model described the median (Figure1) and variability (not shown) well, and consisted of an indirect response model with positive feedback and linear drug effect stimulating wash-out of MADRS (Figure 2).
- Esketamine was found to be ~5x more potent than ketamine, but the estimate should be regarded with caution as study effects cannot be ruled out.

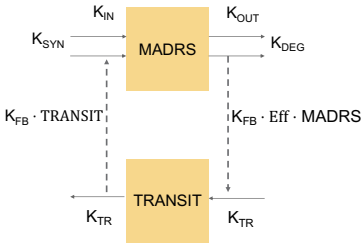

Figure 2. *The final model structure. K_{SYN} is the biomarker production rate and K_{DEG} is the degradation rate.*

- Observed 2W ketamine (0.5 mg/kg) showed similar/slightly better effect than 3W, but a tolerance model did not improve the description of the data. The rapid decrease within 2h after the first dose, and subsequent slower decrease over 4 weeks treatment were predicted well (Figure 1). The stable or slowly increasing MADRS score was also predicted by the model during the follow-up (~18 days).

Table 1. *Final parameter estimates and (RSE%)*

Parameter	Slope (/ng/mL)	Turnover (h)	Base MADRS	K_{FB} (h)	K_{TR} (h)	Placebo effect	Esketamine on Slope	additive RUV		
								MADRS	Placebo	Placebo CFB
Typical	425 (44)	68 (110)	34 (2.2)	7 (85)	0.27 (25)	0.82 (3.3)	-0.8 (16)	3.6 (61)	2.8 (16)	1.1 (61)
IIV %	45 (85)	240 (22)	11 (16)		136 (20)	16 (22)				

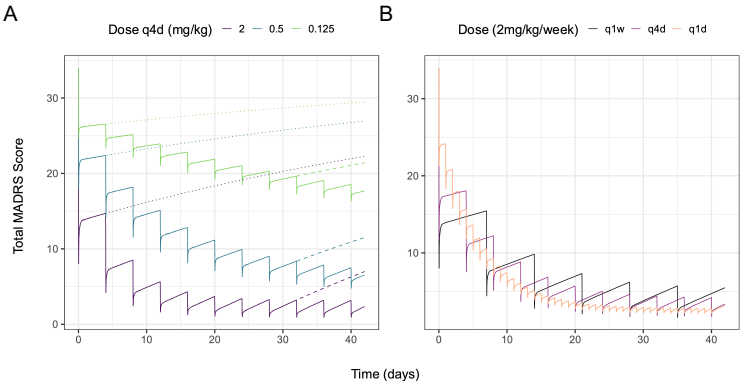

Figure 3. *Typical simulations of MADRS score after (A) 0.125, 0.5, 2 mg/kg of ketamine (40 minute IV infusion) as a single dose (dotted), 4 weeks of dosing (dashed) or 6 weeks (solid) and (B) as total weekly dose of 2 mg/kg given once daily, every fourth day or once weekly for 6 weeks.*

Simulations showed the average long-term effect to be insensitive to dosing interval (Figure 3), and was rather governed by the total weekly dose. However, higher doses given less often created a faster onset of effect, while dividing the dose into more frequent administration smoothed the response profile.

References

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