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Introduction

- Major depressive disorders present a major clinical challenge with current antidepressant treatment achieving remission in only approximately 30% of patients [1].
- Several recent trials suggested that a subanaesthetic dose of ketamine could provide a significant antidepressant effect in patients with depression (e.g.[2, 3, 4]); however, most studies have given ketamine at a fixed dose (0.5 mg/kg).
- A recently reported dose-titration pilot study by Loo et al. [4] evaluated low doses of ketamine administered across multiple routes of administration (IV, SC, IM) in patients with treatment refractory depression. This analysis uses the PKPD data reported in by Loo et al. [4] to characterize the population PKPD relationships for the effect of ketamine on the Montgomery–Asberg Depression Rating Scale (MADRS scores) and cardiovascular side effects of blood pressure and heart rate.

Aims

The aims of this work were to:

- Develop population PKPD models that can effectively describe ketamine and norketamine (metabolite) PKPD relationships for MADRS scores, blood pressure and heart rate after IV, SC, and IM administration of ketamine in patients with treatment-refractory depression.
- Identify covariates that are predictive for the PK/PD of ketamine.
- Present the PKPD models as a web application to facilitate interactive decision support of the use of ketamine to treat depression.

Methods

- PKPD data were collected from an active placebo-controlled pilot study in which 21 treatment-refractory depressed participants received ketamine (dose titration 0.1-0.5 mg/kg) by either IV, SC, or IM administration.
- Model development employed non-linear mixed effect modelling using NONMEM.
- Population PK models for ketamine and norketamine were first established and then used for subsequent PD modelling of the MADRS scores (PD metric for the antidepressant effect), blood pressure and heart rate data (PD metrics for ketamine side effects).
- The final PKPD models of ketamine MADRS scores, blood pressure, and heart rate were implemented as a Shiny app.

Results

- Overall, there were 21 subjects providing a total of 278 ketamine, 278 norketamine concentrations, 314 MADRS, 320 blood pressure, and 322 heart rate observations.
- The PK for ketamine and norketamine were best described using two-compartment model with first-order absorption after SC and IM administration with allometric scaling on all clearance and volume of distribution parameters (Table 1).
- For all PD effects, models of ketamine alone were superior to models with norketamine concentration linked to an effect.
- Ketamine PD effect on MADRS scores was best described by a turnover proportional Emax model. Blood pressure and heart rate were best described by an immediate effect, additive Emax models (Table 2).
- The pcVPC plots show that the final PKPD models had a good predictive performance for the observed data (Figure 1).
- Estimated EC50 from MDRDS score, blood pressure, and heart rate PD models were 0.439, 468, and 7580 ng/ml, respectively. This suggests that ketamine has a potent antidepressant effect and remission criteria can be achieved at low plasma concentrations (small EC50) far below the EC50 for cardiovascular side effects.

Shiny app

- The shiny application for the final ketamine PKPD models for MADRS scores, blood pressure and heart rate can be accessed at (<https://acp-unisa.shinyapps.io/ketaminepkpd/>, QR code above). The application has not been validated clinically and is an example of how PKPD modelling can be used to develop dosing regimens.

Table 1. Final parameter estimates of the PKPD models

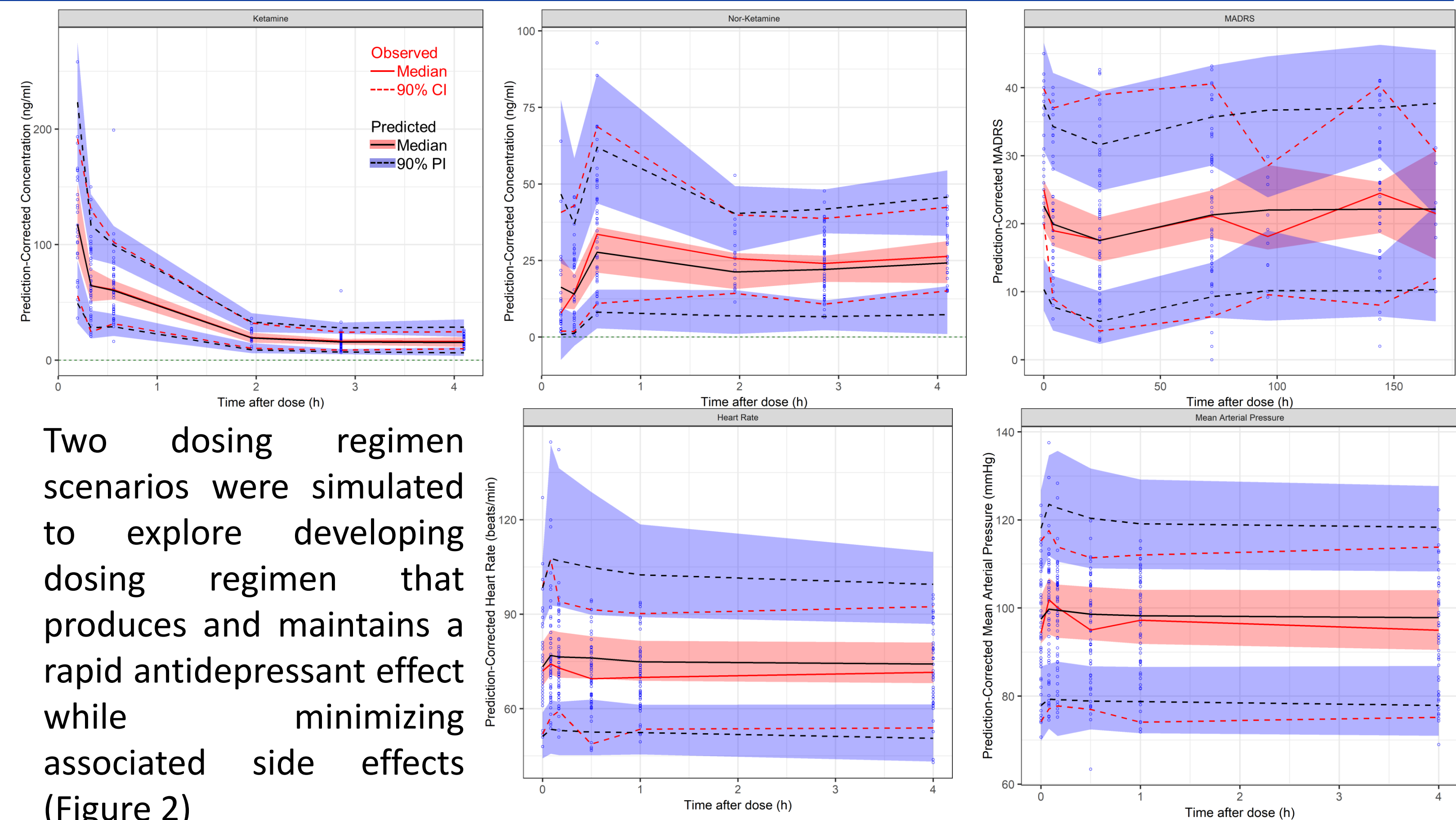
Code	Description	Unit	Pop value ^a	%RSE	BSV (SD)	%RSE	ETA p-value	Shrinkage (%)
<i>CL_{ketamine}</i>	Central clearance of ketamine	L/h	69.6	10.5	0.185	11.1	0.356	9.7
<i>V1_{ketamine}</i>	Central volume of distribution of ketamine	L	79.3	18.7	0.468	15.1	0.846	7.1
<i>Q_{ketamine}</i>	Intercompartmental clearance of ketamine	L/h	121	14.3				
<i>V2_{ketamine}</i>	Peripheral volume of distribution of ketamine	L	87.4	14.8	0.427	23.7	0.672	22.2
<i>KA_{ketamine}</i>	Absorption rate constant	h ⁻¹	6.53	19.1				
<i>F_{extrovascular}</i>	Bioavailability from subcutaneous and intramuscular routes	unitless	0.644	11.5	-	-	-	-
<i>CL_{norketamine}</i>	Central clearance of norketamine	L/h	30.3	31.2	0.651	19.1	0.476	
<i>V1_{norketamine}</i>	Central volume of distribution of norketamine	L	73.6	12.4	0.466	22.4	0.811	16.3
<i>Q_{norketamine}</i>	Intercompartmental clearance of norketamine	L/h	54.2	11.3				16.2
<i>V2_{norketamine}</i>	Peripheral volume of distribution of norketamine	L	339	34.2				
<i>RUVPROP-ketamine</i>	Proportional residual error	Ratio	0.294	9.6	-	-	-	-
<i>RUVADD-ketamine</i>	Additive residual error of ketamine	ng/ml	0.00001	-	-	-	-	-
			FIX					
<i>RUVPROP-norketamine</i>	Proportional residual error	Ratio	0.257	18.6	-	-	-	-
<i>RUVADD-norketamine</i>	Additive residual error of norketamine	ng/ml	3.88	14.7	-	-	-	-

		MADRS scores		Blood Pressure		Heart rate	
Code	Description	Pop value ^a	%RSE	Pop value ^a	%RSE	Pop value ^a	%RSE
<i>BASE</i>	Baseline MADRS, blood pressure, or heart rate	22.3	0.27	97.1	0.11	72.7	0.16
<i>EC50</i>	Ketamine concentration at half maximum effect	0.439	2.13	468	1.85	7580	1.5
<i>EMAX</i>	Maximum drug effect	1	Fix	51.6	2.43	220	FIX
<i>HILL</i>	Hill coefficient	-	-	2.04	1.14	-	-
<i>TURN</i>	Turnover time (h)	42.1	1.63	-	-	-	-
<i>PPV_BASE</i>	Population parameter variability on baseline (SD)	0.277	0.97	0.103	0.70	0.152	0.73
<i>PPV_EC50</i>	Population parameter variability on EC50 (SD)	-	-	0.60	2.6	1.56	1.5
<i>PPV_TURN</i>	Population parameter variability on Turnover time (SD)	0.917	1.71	-	-	-	-
<i>RUV_ADDPD</i>	Additive residual error	5.15	0.40	6.98	0.44	9.15	0.8
<i>RUV_PROPPD</i>	Proportional residual error model (ratio)	0.0001	FIX	0.0001	FIX	0.0001	FIX

^a Population typical value.SD: standard deviation; %RES: percent of relative standard error.

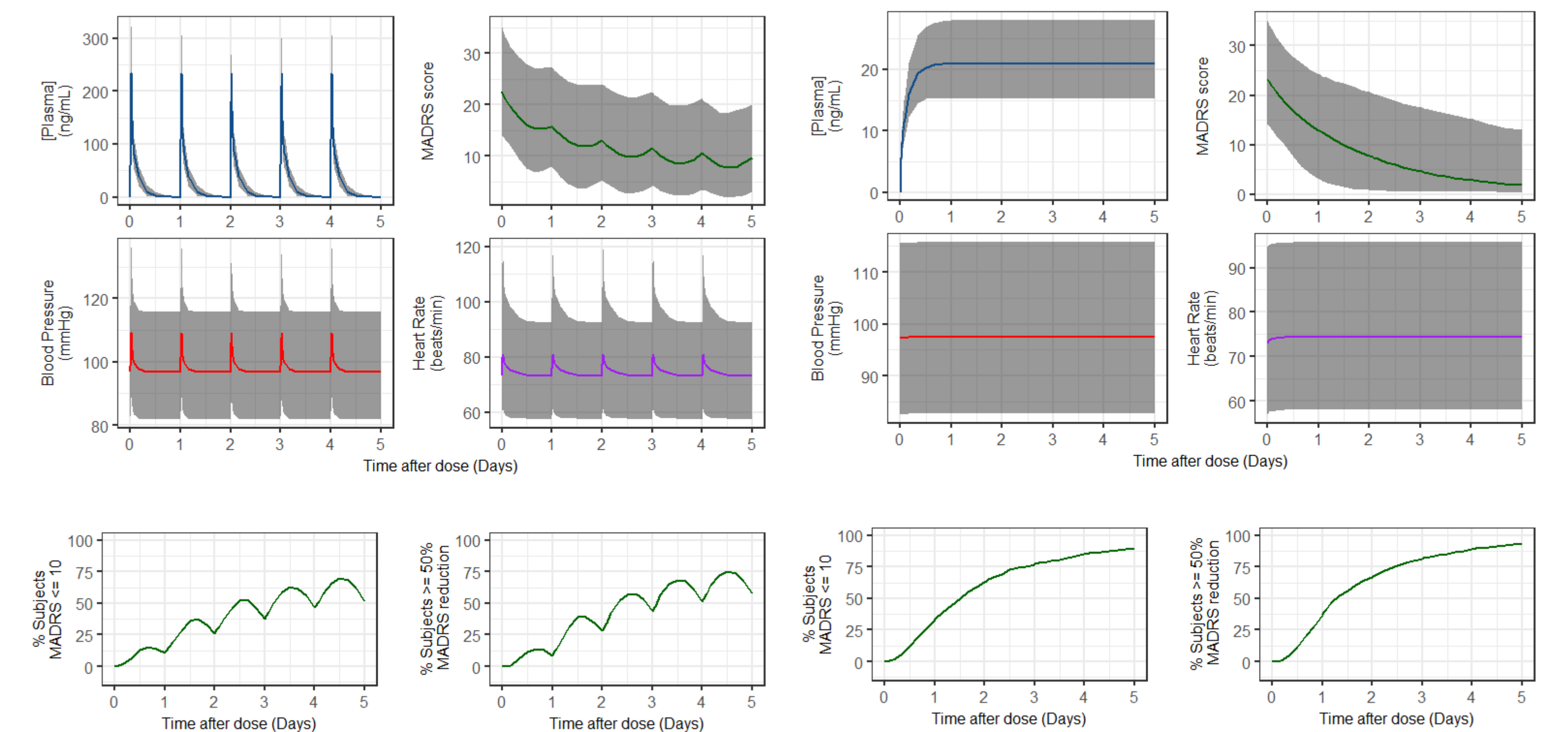
Units for blood pressure, heart rate, and ketamine concentration are mmHg, beats/min, and ng/mL, respectively.

Figure 1. pcVPC for ketamine, norketamine, MADRS scores, blood pressure and heart rate in patients receiving ketamine.



Two dosing regimen scenarios were simulated to explore developing dosing regimen that produces and maintains a rapid antidepressant effect while minimizing associated side effects (Figure 2)

Figure 2. Simulated dosing scenarios for ketamine, MADRS scores, blood pressure and heart rate in patients receiving: 0.5mg/kg ketamine IV infusion over 40 minutes every day for 5 days (left), or same dosing regimen infused over 24 hours (right).



Conclusion

- PKPD models’ simulations suggest that a low-dose continuous delivery of ketamine can potentially be a promising method for ketamine administration as the antidepressant effect can be achieved at low plasma concentrations which are far below the concentrations required to produce any significant cardiovascular side effects.
- The shiny web application of the population PKPD models can be used as a practical tool for optimizing the antidepressant - side effects trade-off for ketamine.

References

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