KETAMINE AND NOT ITS PHARMACOLOGICALLY ACTIVE METABOLITE NORKETAMINE MEDIATES CNS EFFECTS IN HEALTHY VOLUNTEERS

Safai Pour A[1], van Mechelen JC[1], Wieles T[1] , Borghans LGJM[1], Otto M[1], van Noorden MS[2], Harmer CJ[3], Gillespie A[3], van Gerven JMA[1,2], Jacobs GE[1, 2]

1 Centre for Human Drug Research (CHDR), Leiden, the Netherlands
2 Leiden University Medical Center (LUMC), Dept. of Psychiatry, Leiden, Tthe Netherlands
3 University Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

Introduction

- Single intravenous (IV) doses of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (KetIV) demonstrate rapid but transient antidepressant (AD) efficacy in treatment resistant major depressive disorder (TR-MDD)[1].
- KetIV maintenance treatment is therefore indicated but repeated KetIV administration is burdensome.
- Oral ketamine (KetPO) is currently under investigation as potential maintenance treatment following response to KetIV in TR-MDD[2].
- First-pass metabolism is however expected to alter plasma ketamine (KET)/norketamine (NK)[3] ratios after PO administration, which is relevant since norketamine is pharmacologically active.
- KetPO's pharmacokinetic (PK) and pharmacodynamic (PD) profiles are not well-characterized.

- **This study characterized the PK, PD, and safety profiles of KetPO and KetIV in healthy volunteers.**

Methods

- Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over study with esketamine in 16 healthy volunteers.
- Treatments: KetPO 0.2mg/kg, 0.45mg/kg, KetIV 0.4mg/kg infusion over 40 minutes and placebo.
- PK profiles determined.
- PD characterized central nervous system (CNS) test battery (Neurocart), quantitative electroencephalography (qEEG), and Mystical Experiences Questionnaire (MEQ-30).
- Safety assessments: adverse events (AEs), clinical lab tests, 12-lead electrocardiogram (ECG), vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS).
- PD measurements analyzed up to 6 hours post dose with mixed model analysis of covariance .
- Non-compartmental PK analysis of esketamine and its active metabolites up to 24 hours post dose.

Results

- 8 males and 8 females included, average age 27 (21-35), average BMI: 23 (19-27) kg/m2
- Mean maximal plasma concentrations (C_{max}) for KET and NK were 9.8 and 62.0 ng/mL (KetPO, 0.2 mg/kg), 22.7 and 127.3 ng/mL (KetPO, 0.45 mg/kg), and 145.5 and 55.2 ng/mL (KetIV), respectively (**Figure 1**).
- Compared with placebo, KetIV demonstrated robust PD effects while these were limited and absent for KetPO 0.45 mg/kg and 0.2 mg/kg, respectively (**Table 1**).
- No serious AEs, most AEs mild and self-limiting
- Most frequent AEs: dissociation, euphoria, nausea/vomiting (KetIV); euphoria (KetPO)
- Moderate and transient BP and heart rate increases with KetIV, KetPO did not affect BP

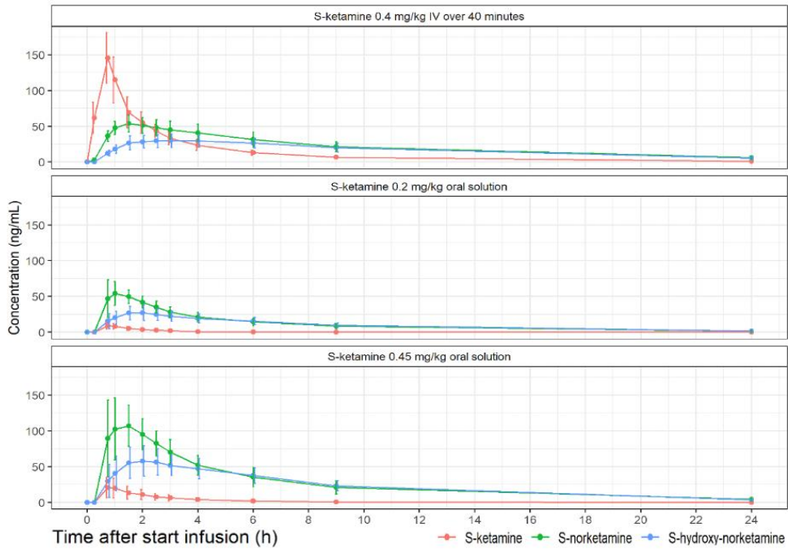

Figure 1: Mean (SD) plasma concentration-time profiles over time (0 – 24h) for esketamine, esnorketamine and hydroxy-noresketamine.

Summary of Least Square Mean (LSM) analysis results up to 6 hours post dose			
		S-ketamine 0.4 mg/kg IV vs Placebo	S-ketamine 0.45 mg/kg vs Placebo
Neurocart			
assessment	**functional CNS domain**	**Estimated difference (95% CI); p-value**	
Saccadic peak velocity (degrees/s)	vigilance /arousal	-25.60 (-38.20, -13.00) p=0.0002	-5.72 (-18.40, 6.95) p=0.3665
Smooth pursuit eye movements (%)		-11.37 (-14.29, -8.44) p=<.0001	-3.26 (-6.17, -0.34) p=0.0295
Body sway (mm)	postural stability	18.4% (2.4%, 37.0%) p=0.0238	1.3% (-12.1%, 16.7%) p=0.8531
Adaptive tracking (%)	sustained attention	-1.985 (-3.616, -0.354) p=0.0182	0.432 (-1.200, 2.064) p=0.5963
VAS Alertness (mm)	subjective sedation	-3.7 (-5.1, -2.4) p=<.0001	-0.4 (-1.7, 1.0) p=0.5671
VAS Feeling High log (mm)	subjective high	0.4945 (0.4110, 0.5780) p=<.0001	0.1676 (0.0848, 0.2503) p=0.0002
VAS Mood (mm)	subjective euphoria	1.8 (0.4, 3.1) p=0.0100	0.6 (-0.8, 1.9) p=0.4105
Quantitative electroencephalography (qEEG)		**Estimated difference (95% CI); p-value**	
qEEG Alpha-power		-21.5% (-33.1%, -8.0%) p=0.0031	-15.0% (-27.2%, -0.7%) p=0.0405
qEEG Beta-power		-22.1% (-32.1%, -10.6%) p=0.0006	-17.4% (-27.7%, -5.5%) p=0.0061
qEEG Delta-power		-20.4% (-32.8%, -5.7%) p=0.0092	-16.2% (-29.2%, -0.8%) p=0.0408
Psychomimetic effects		**Estimated difference (95% CI); p-value**	
MEQ-30 Total Score		1.3 (0.9, 1.7) p=<.0001	0.2 (-0.2, 0.6) p=0.2883

Table 1: Pharmacodynamic analysis up to 6 hours post dose. VAS: Visual Analogue scale; MEQ: Mystical Experiences Questionnaire

Conclusions

- Plasma KET C_{max} was ~15 times higher with KetIV compared with KetPO 0.2mg/kg at similar NK concentrations.
- KetIV showed significant sedative, psychomotor and psychomimetic effects up to 6 hours post dose; KetPO 0.2mg/kg lacked PD effects.
- KetPO 0.45mg/kg's PD effects were limited and its AE profile distinct from KetIV, despite its NK plasma concentrations approximately double that of both KetIV and KetPO 0.2 mg/kg.
- Both KetPO and KetIV administrations were safe.

- **KET and not NK primarily mediates CNS effects in humans.**
- **Since KetPO's efficacy as maintenance treatment in TR-MDD not yet established, it's PK profile should inform future study design.**

CHDR
Centre for Human Drug Research

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl

1. Murrough et al. Am. J. Psychiatry. 2013; 170: 1134–1142.
2. Smith-Apeldoorn et al. BMC Psychiatry. 2019; 19 (375).
3. Fanta et al. Eur J Clin Pharmacol. 2015; 71 (4): 441 – 447.