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Pharmacokinetic properties of *S*-ketamine and ketamine racemate after dry powder inhalation, intravenous and intratracheal administration in rats

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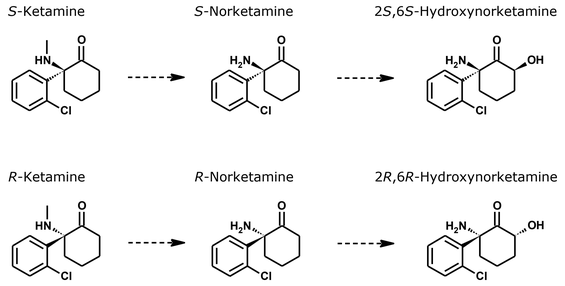
Introduction

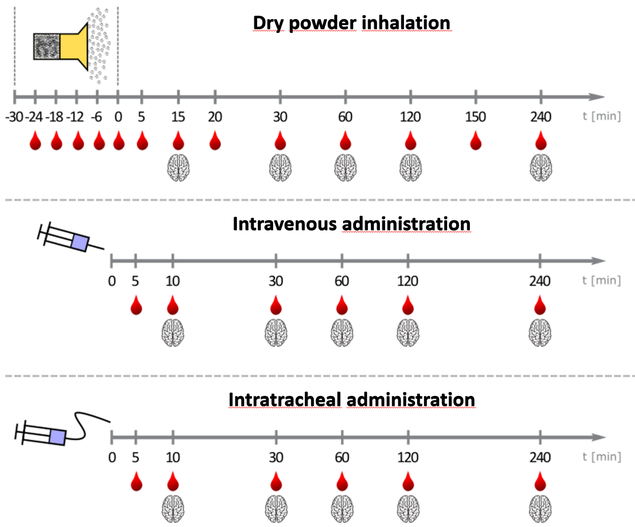
Ketamine has been known and used as anaesthetic for over 50 years. Recently, it is getting more and more attention as a very rapid acting antidepressant being considered as a promising treatment option for patients suffering from treatment-resistant depression. However, ketamine undergoes a strong first-pass metabolism effect, excluding possibility of oral administration from drug development process. Infusion of the ketamine as a therapeutic option requires an outpatient support. In order to develop a reliable and comfortable ketamine delivery method, we explored the pharmacokinetic characteristics in rats of *S*-ketamine as a single enantiomer and compared with racemic ketamine applying different administration routes: intravenous, intratracheal and dry powder inhalation. The inhalation route of administration could provide a novel solution for ketamine delivery and may offer additional advantages including efficient and precise dosing and comfortable, preferable administration over intravenous route.

Ketamine metabolism

Simplified scheme of enantiomer specific metabolism of (*S,R*) - Ketamine



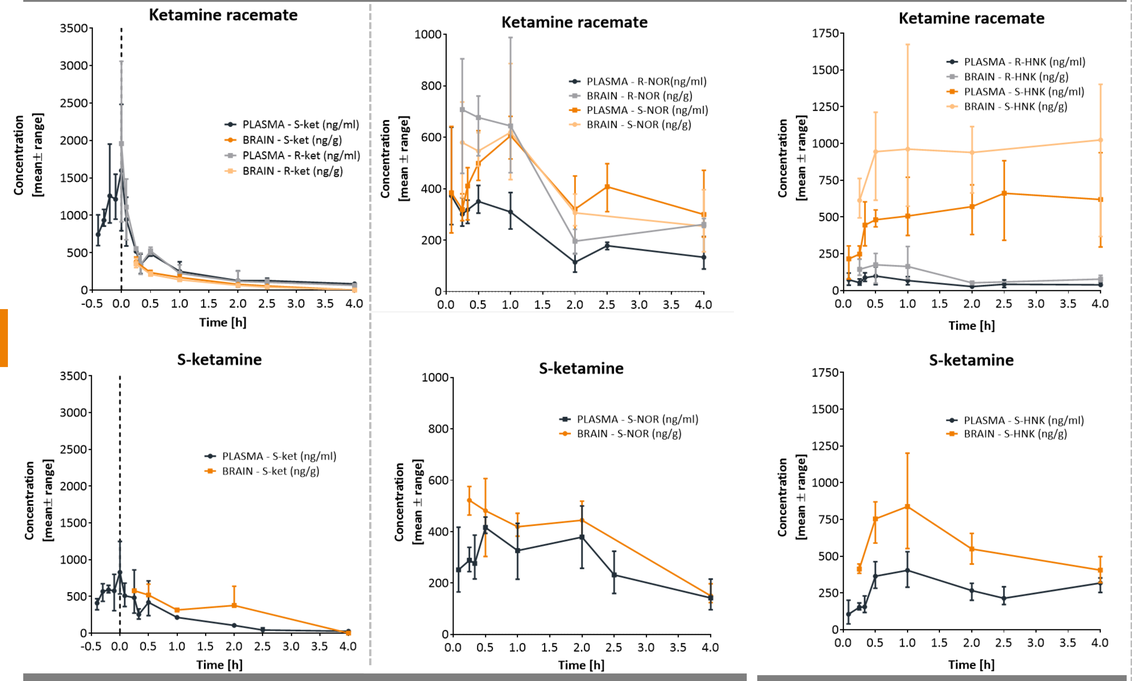
PK study plan



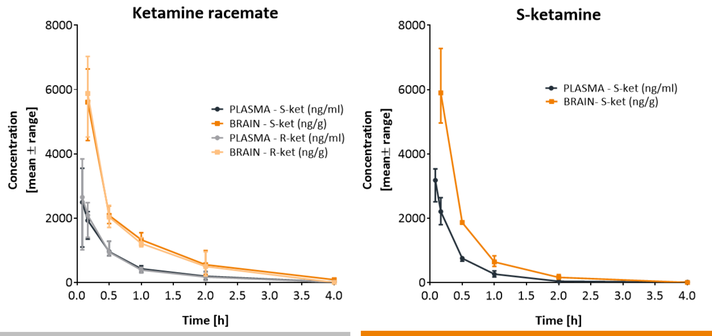
	Administration				
	Inhalation		Intravenous		Intratracheal
Dose	*S*-ketamine	Racemate	*S*-ketamine	Racemate	*S*-ketamine
Estimated [mg/kg]	10	20	10	20	10
Achieved[mg/kg]	7,8	19,9	-	-	-

Pharmacokinetics

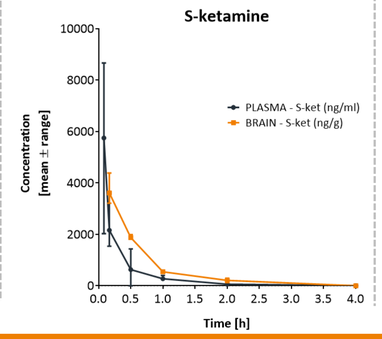
Dry powder inhalation



Intravenous administration



Intratracheal



C_{max} and t_{max} paramaters for plasma				
Administration	Test Item	Analyte	C_{max} [ng/ml]	t_{max} [min]
Inhalation	*S*-ketamine	*S*-ketamine	828±243	0
	Racemate	*S*-ketamine	1598±572	0
		R-ketamine	1958±712	0
Intravenous	*S*-ketamine	*S*-ketamine	3179±580	5
	Racemate	*S*-ketamine	2494±1258	5
		R-ketamine	2653±1466	5
Intratracheal	*S*-ketamine	*S*-ketamine	5750±3393	5

C_{max} and t_{max} paramaters for brain tissue				
Administration	Test Item	Analyte	C_{max} [ng\g]	t_{max} [min]
Inhalation	*S*-ketamine	*S*-ketamine	577±35	15
	Racemate	*S*-ketamine	379±57	15
		R-ketamine	352±65	15
Intravenous	*S*-ketamine	*S*-ketamine	5899±1221	10
	Racemate	*S*-ketamine	5608±1121	10
		R-ketamine	5875±1264	10
Intratracheal	*S*-ketamine	*S*-ketamine	3612±671	10

Selected parameters for *S*-ketamine							
Administration	Test Item	$AUC_{(0-t)}$ [ng*h/L]	F	$t_{1/2}$ [min]	k_{el} [1/min]	V_D [l]	Cl_{tot}[L\min]
Inhalation	*S*-ketamine	867	85%	-	-	-	-
	Racemate	1383	85%	-	-	-	-
Intravenous	*S*-ketamine	1315	-	39,31	0,0176	4,68	0,032
	Racemate	1648	-	40,53	0,0171	1,76	0,026
Intratracheal	*S*-ketamine	1259	96%	-	-	-	-

METHODS

***In vivo*:** The pharmacokinetic parameters were evaluated in male Wistar rats (n = 3 per timepoint) following single intravenous, intratracheal or dry powder inhalation of either S-ketamine or ketamine racemate (in the form of hydrochloride) using 10 mg/kg and 20 mg/kg doses respectively. Dry powder inhalation of ketamine powder lasted for 30 minutes. For i.v. and i.t. administration both compounds was dissolved in saline. For blood collection each rat was bled by jugular venipuncture and the samples were collected into tubes containing the anticoagulant, EDTA and centrifuged to obtain plasma. Blood collection was carried out at 6 timepoints for i.v. and i.t. administration and at 13 timepoints (4 during inhalation) for dry powder inhalation. Brain tissues were dissected at 5 occasions post-administartion.

Sample preparation: 50ul of plasma or brain homogenate samples were extracted with 150ul of internal standard (Ketamine-d4) solution in acetonitrile. Samples were vortexed for 1min and centrifuged for 4 min. Extracts were analyzed by LC-MS/MS.

LC-MS/MS methods description: For ketamine S- and R-enantiomers resolution Chiralpak AGP (150x3 mm; 5 µm) column was used with isocratic elution of 10mM ammonium acetate (pH 7.1):acetonitrile (92:8, v:v) as a mobile phase. Flow rate was set at 0.5 mL/min. Calibration curve range was 25-5000 ng/mL with LLOQ 25 ng/mL. Ketamine metabolites R,S-norketamine, (*2S,6S*)-hydroxynorketamine, (*2R,6R*)-hydroxynorketamine and *R,S*-dehydronorketamine separation was achieved on a chiral Lux® 3 µm Amylose-2 column (250x4.6 mm) with a mobile phase consisting of 10mM ammonium acetate pH 9.0, acetonitrile and 2-propanol (70:10:20 v:v:v). The flow rate was set at 0.5 mL/min. The LLOQ values were determined as 12.5 ng/mL for all of metabolites. Linearity of the method was evaluated within the range of 12.5-2500 ng/mL. Both studies were performed with the use of Agilent 6460 mass spectrometer as a detector.
The study received the approval of the respective Local Bioethics Committee.

Pharmacokinetic calculations and statitistics: Pharmacokinetic calculations considered one-compartmental model and selected parameters were calculated with WinNonLin software. Statistical analysis was done using GraphPad Prism v7.0.

CONCLUSIONS

- Dry powder inhalation administration provided satisfying systemic and brain tissue exposure with the 85% bioavailability for both *S*-ketamine and racemate dosing.
- Intravenous and intratracheal administration provided a comparable pharmacokinetic profile with very high, 95%, bioavailability for IT route.
- Dry powder inhalation proved to be a very convenient delivery method for ketamine with high bioavailability – contrary to available data for oral administration, after which ketamine undergoes extensive first-pass metabolism.
- The inhalation route of administration could provide a novel solution for ketamine delivery and offer additional advantages including efficient and precise dosing and comfortable, preferable administration over intravenous route.

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