Ketamine pharmacometrics

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Are the psychedelic and analgesic effects of ketamine independent?

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Submitted

Ketamine is a versatile drug that is used by anesthesiologists, pain physicians and more recently also by psychiatrists.[1] At high dose, ketamine produces a dissociative anesthetic state, while at low (subanesthetic) doses it produces potent analgesia. Additionally, ketamine produces psychedelic effects related to its dissociative properties. At low doses these dissociative effects cause inner feelings and thoughts that do not agree with reality, and misperception of external stimuli such as abnormal alterations of the extremities or aberrant experience of time and surroundings.[2] At increasing doses overt paranoia, hallucinations, severe derealization and depersonalization, and anxiety attacks may occur.[2] Due to these serious adverse effects, pain physicians are often hesitant to consider ketamine for treatment of chronic pain and patient compliance can be low due to fear of dissociation. It has been suggested that ketamine analgesia (and antidepressant properties) is highly associated and possibly even generated by its dissociative effects.[3-5] This would suggest that ketamine (and its metabolites) dissociative and analgesic effects have common pharmacodynamic properties with a similar potency and onset/offset time. However, there is evidence that suggests that the two endpoints are independent. For example, in healthy volunteers, Gitlin et al.[6] recently studied the effect of ketamine on cuff pain intensity and psychedelic symptoms without and with co-administration of midazolam. Their statistical analysis revealed that analgesia was not associated with the dissociative effects of ketamine. This indirect evidence agrees with earlier findings from our laboratory that showed that the nitric oxide donor sodium nitroprusside modestly reduced psychedelic symptoms in volunteers receiving racemic ketamine but not esketamine.[7] Such an effect was not observed for ketamine analgesia (unpublished observation). To determine whether ketamine-induced dissociation and analgesic behavior are independent, we performed a population pharmacokinetic-pharmacodynamic analysis in healthy volunteers.[8] All subjects received increasing doses of racemic ketamine and pain relief to a pressure pain stimulus was measured concomitantly with signs of alterations in perception of external stimuli. Our Null hypothesis is that ketamine pharmacodynamics (potency and onset/offset times) are equal for these two endpoints, an indication that dissociation and analgesia from ketamine are interdependently generated in the brain.

METHODS

Ethics and subjects

The data used in this analysis is part of a larger data set that was used previously to study the effects of sodium nitroprusside (SNP) on ketamine-induced adverse effects,[7] to construct a population pharmacokinetic model of ketamine and its metabolites,[8] and a pharmacodynamic model of ketamine-induced changes in cardiac output.[9] In the

current analysis, we developed a population pharmacodynamic model of ketamine and its metabolite norketamine to describe the relation between racemic (*RS*) ketamine and norketamine plasma concentrations and pressure pain threshold and the change in external perception as measure of ketamine psychedelic effect. The study protocol was approved by the institutional review board (METC LDD, Leiden University Medical Center, Leiden, The Netherlands) and registered at the trial register of the Dutch Cochrane Center (www.trialregister.nl) under registration number 5359. The study was performed in healthy male volunteers aged 18-34 years and a body mass index in between 20 and 30 kg/m^2. Specific inclusion and exclusion criteria are found in Ref. 7.

Study design

The original study was a 4-arm randomized double-blind study during which esketamine or *RS*-ketamine were infused against a background of either SNP or normal saline (placebo).

For the current analysis we used data obtained on a single occasion on which subjects received escalating intravenous doses of *RS*-ketamine (Ketalar, Pfizer, Germany) over 3 hours (first hour 0.28 mg/kg, second hour 0.57 mg/kg and third hour 1.14 mg/kg) against a background of normal saline infusion.

The following data were collected prior and during *RS*-ketamine infusion:

(1) The pain pressure threshold was measured was by applying an increasing pressure to a 1 cm^2 skin area between thumb and index finger, using the FP 100 N Algometer (FDN 100, Wagner Instruments Inc, CT, USA). The applied pressure was gradually increased until the subject indicated when the pressure became painful, after which the pressure was released. The FDN 100 has a force capacity (± accuracy) of 100 ± 2 N and graduation of 1 N. Pressure pain thresholds were obtained before start of the *RS*-ketamine infusion (baseline), followed by measurements at 15 min intervals during and after *RS*-ketamine infusion. Measurements continued until 2 h after termination of the *RS*-ketamine infusion.

(2) External perception was obtained from the Bowdle questionnaire.[10] The Bowdle questionnaire is a validated list of 13 items developed to quantify the psychedelic effects of ketamine in healthy volunteers. The subject is asked to rate each item on a 100 mm visual analogue score that range from "not at all" to "extremely". External perception relates to the misapprehension of external stimuli or the surroundings including body parts and is derived from the following items: my body or body parts seemed to change their shape or position; my surroundings seemed to change in size, depth, or shape; the passing of time was altered; the intensity of colours changed; and the intensity of sound changed. External perception was measured at t = 0 (baseline) and 20, 40, 55, 80, 100, 115, 140, 160, 175, 200, 220, 240, 260 and 280 after the start of ketamine infusion.

(3) Plasma concentrations of *R*- and *S*-ketamine and *R*- and *S*-norketamine. At regular time points (t = 0, baseline) and 2, 6, 30, 59, 62, 66, 100, 119, 122, 126, 150, 179, 182, 186, 195, 210 and 300 min after the start of ketamine infusion) 8 mL blood was drawn from an arterial line placed in the radial artery (opposite to the infusion arm). Plasma samples were measured in the laboratory of dr. Evan Kharasch (Washington University School of Medicine, St. Louis, MO, USA) as described by Rao et al.[11]

Data analysis

Model development

The pharmacokinetic data were analyzed separately and previously reported.[8] From that model, Empirical Bayesian Estimates (EBE's) of the PK parameters were obtained and their fixed values were used as input to the pharmacodynamic model.

Pressure pain threshold (PPT) and external perception (ExP) were simultaneously analyzed in a single model. Pressure pain was modelled as:

$$PPT(t) = BLN * [1 + (C\mathit{RS}\text{-}K(t)/C50\text{-}K)^{\gamma}] \quad \text{Eqn(1)}$$

where PPT(t) is the amount of pressure in Newton applied at which the subjects first reported pain, BLN is the estimated pressure pain threshold at baseline, C*RS*-K the plasma concentration of *RS*-ketamine in nmol/mL (*i.e.* the sum of the *R*- and *S*-isomers), C50-K is the estimated *RS*-ketamine concentration needed to increase the PPT by 50% but analgesia by 100% (in nmol/mL),[12] and γ the Hill coefficient. External perception was described by a sigmoid Emax model:

$$ExP(t) = [Emax * C\mathit{RS}\text{-}K(t)^{\gamma}] / [C50K^{\gamma} + C\mathit{RS}\text{-}K(t)^{\gamma}] \quad \text{Eqn(2)}$$

where ExP is the experienced level of external perception as rated on a 100 mm visual analogue scale, Emax the maximum effect on external perception (100), C50K the *RS*-ketamine concentration in nmol/mL needed to reach 50% of Emax and γ the Hill coefficient. Since external perception was measured on a 100 mm VAS scale, ratings could not be higher than 100 points. We therefore incorporated the M3 data censoring method as published by Beal et al.[13] for the external perception data.

Since we observed a small discrepancy in the individual model fits for ExP and to a lesser extent for PPT during the infusion phase, we postulated that an *RS*-norketamine effect might be present. We therefore added *RS*-norketamine as input to the model, based on a receptor kinetics approach, in which *RS*-norketamine could displace *RS*-ketamine from the receptor. The consequence of this would be a counteracting effect of *RS*-norketamine on the effects of *RS*-ketamine.[14] The effect of *RS*-norketamine was defined as:

EFF*RS*-NK = C*RS*-NK/C100NK Eqn(3)

where C*RS*-NK is the *RS*-norketamine plasma concentration in nmol/mL and C100NK the *RS*-norketamine plasma concentration causing a 100% increase in C50K. So in equations (1) and (2) above, C50K was substituted by

C50KN = C50K * (1 + EFF*RS*-NK) Eqn(4)

To account for a possible delay between plasma concentrations and effect, effect compartments for *RS*-ketamine and *RS*-norketamine were postulated that were assumed to equilibrate with the central compartment with an effect half-time of $t_{1/2} = \ln(2)/k_{e0}$, where k_{e0} is the rate constant.

Covariates

Since pressure pain and external perception were simultaneously analyzed, potential differences in estimated C50 and k_{e0} parameter estimates between PPT and ExP were tested, by using an automated covariate search algorithm (Stepwise Covariate Model building module from PsN), with the measured outcome (*i.e.* pressure pain *vs* external perception) as potential covariate.

The first selection step incorporated a forward selection approach, in which covariates were first one by one added to the model parameters. The parameter – covariate combinations that caused the largest significant ($p < 0.01$) drop in the objective function value (OFV) was added first, followed by other parameter-covariate combinations that caused the next largest significant drop in OFV. This process continued until all parameter-covariate combinations were included in the model or until no more parameter-covariate combinations causing a significant drop in OFV were left.

The final forward model was then used for the backward search. In this step, covariates were removed one by one from the model. Covariates were only retained in the model when removal caused a significant ($p < 0.001$) increase in the OFV. This process continued until no covariates that caused a significant worsening in the OFV were left or until all covariates were removed from the model. For the backward search, a more stringent selection criterium ($p < 0.001$) was used in order to prevent irrelevant parameter-covariate combinations to be included in the model. A linear relation was used to add covariate effects to the model parameters: $\theta_i = \theta_{ref} \times (1 + \theta_{COV})$, with the typical parameter value for a subject with the reference outcome θ_{ref} (pressure pain) and the effect of belonging to the non-reference category θ_{COV} (external perception).

Statistical analysis

Data analysis was performed with NONMEM version 7.4.4 (ICON Development Solution, Hanover, Maryland). To account for interindividual variability, random effects were included in the model in an exponential relation: $\theta_i = \theta \times \exp(\eta_i)$, where θ_i is the parameter for individual i, θ the population parameter and η_i is the random difference between the population and individual parameter. In addition to the $COV step in NONMEM to determine the standard error of the (parameter) estimate, PsN's log likelihood profiling (llp) utility was used to determine the 95% confidence intervals of the for the C_{50} *RS*-ketamine, C_{100} *RS*-norketamine and $t_{1/2}k_{e0}$ parameters.

RESULTS

While all twenty subjects completed the experimental session without serious adverse events, data from three subjects were discarded because these subjects were unable to reliably score the ExP outcome. The mean age ± SD (range) of the remaining 17 subjects was 23 ± 2 (19-28) years, mean weight 82 ± 10 (60-98) kg, height (190 ± 6 (175-193) cm and body mass index 24 ± 2 (20-28) kg/m^2.

The initial model, including only an effect of *RS*-ketamine (absolute objective function (OVF) of 2,671 points) showed a clear underestimation of the ExP and PPT scores in the *RS*-ketamine infusion phase (data not shown). We therefore postulated a *RS*-norketamine effect for both outcomes. Expanding the initial model with *RS*-norketamine, improved the model by 157 OVF points. Since a potential hysteresis between the plasma *RS*-ketamine and *RS*-norketamine concentrations could not be excluded, effect compartments were added to the model. None of the tested covariates were included in the final model. Consequently, for the two endpoints, no differences in C50K, C100NK and k_{e0} could be detected (using one k_{e0} parameter for both compounds significantly improved the model by 42 OVF points). These data indicate that *RS*-ketamine and its metabolite *RS*-norketamine affect PPT and ExP with similar potencies and dynamics, suggestive of high dependency of the two measured endpoints.

Estimated pharmacodynamic parameter estimates are given in Table 1. Plots of the population predicted PPTs and ExP scores *versus* time, goodness of fit plots and a visual predictive check (VPC) based on 1000 simulated datasets are shown in Figures 1-3. All figures show that the model was able to adequately describe the pharmacodynamic data. Log Likelihood profiles (Fig. 4) for the for the C_{50} *RS*-ketamine, C_{100} *RS*-norketamine and $t_{1/2}k_{e0}$ parameters, showed 95% confidence intervals of 0.60-1.09 nmol/ml, 0.33-0.75 nmol/ml and 7.0-19.4 min respectively.

Table 1. Population Pharmacodynamic Parameter values.

	Typical parameter value (SEE) [%CV]	Inter-individual variability (%) (SEE) [%CV]
Baseline pressure pain threshold (N)	60.4 (6.04) [10]	40.4 (3.4) [13]
EMAX *External Perception* (mm)	100 FIX	106.8 (11.7) [11]
γ	4.59 (0.60) [13]	41.1 (8.6) [21]
C50 *RS*-ketamine (nmol/mL)	0.801 (0.192) [24]	-
C100 *RS*-norketamine (nmol/mL)	0.481 (0.154) [32]	25.8 (27.4) [36]
$t_{1/2}k_{e0}$ (min)	12.2 (3.9) [32]	46.9 (8.9) [19]
Additive error pressure pain threshold (N)	9.97 (2.2) [22]	-
Additive error external perception (mm)	5.9 (1.2) [22]	-

EMAX *External Perception* is the maximum possible effect of *External Perception*; γ is a shape parameter; C50 *RS*-ketamine is the estimated *RS*-ketamine concentration causing a 50% increase in pain pressure threshold and C100 *RS*-norketamine the *RS*-norketamine concentration causing a 100% increase in C50K; $t_{1/2}k_{e0}$ is theplasma effect compartment equilibrium half-life for both *RS*-ketamine and *RS*-norketamine.

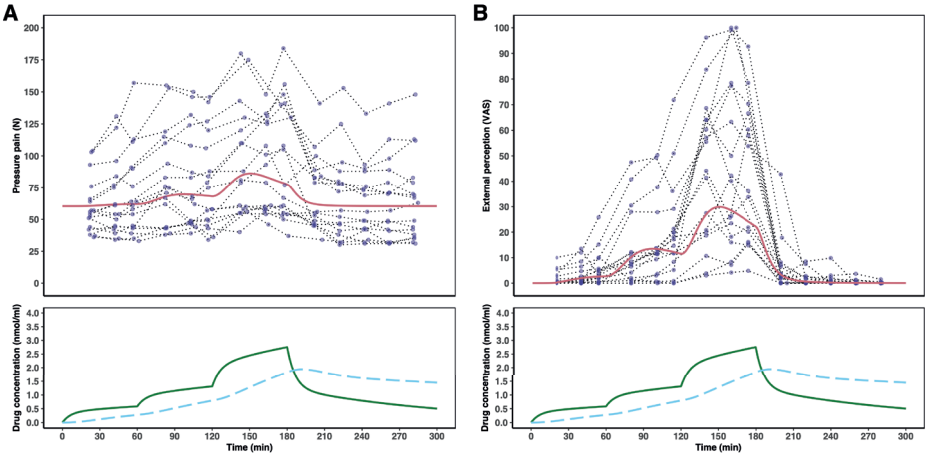

Figure 1. Plots showing the population predicted pharmacodynamic outcomes (red lines) and the observed datapoints for each individual *versus* time (dots and dotted lines) in the upper panels. (**A**) Plot showing pressure pain data and population predicted values and (**B**) plot showing external perception data and population predicted values. The lower two panels show the *RS*-ketamine (green line) and *RS*-norketamine (dashed blue line) concentration time profiles.

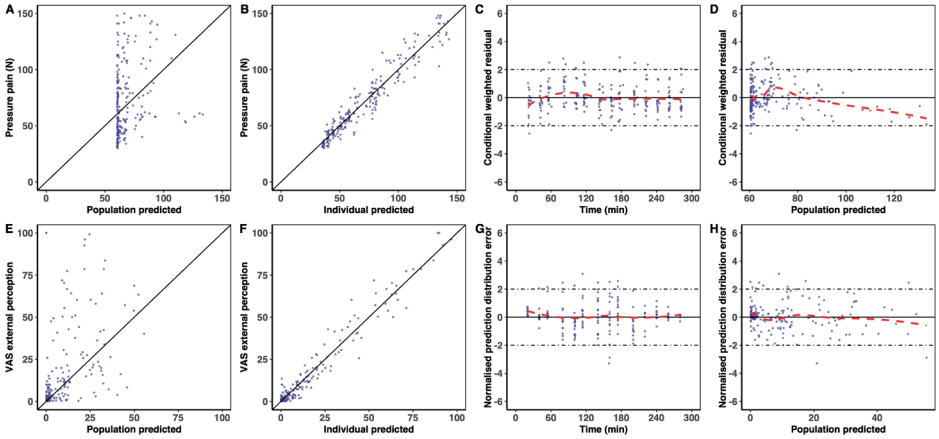

Figure 2. Goodness of fit plots for the population pharmacodynamic model. (**A-D**) Observed *versus* population predicted, observed *versus* individual predicted, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots for pressure pain. (**E-H**) Observed *versus* population predicted, observed versus individual predicted, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots for external perception.

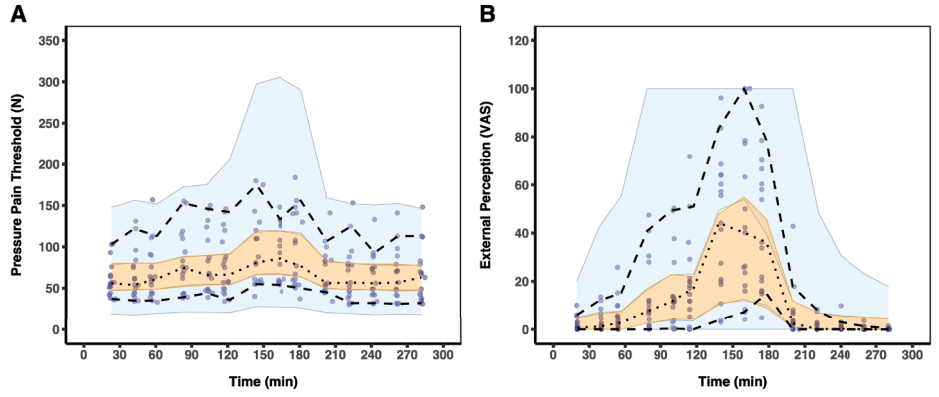

Figure 3. Visual predictive checks for the pressure pain threshold (**A**) and external perception (**B**) data. The middle dotted lines represent the 50th percentile of the observed data. The lower and upper dashed lines show the 5th and 95th percentiles of the observed data respectively. The 95% confidence interval for the 50th percentile of the simulated data is shown by the orange shaded area. The lower and upper gray shaded areas represent the 95% confidence intervals for the 5th and 95th percentiles of the simulated data.

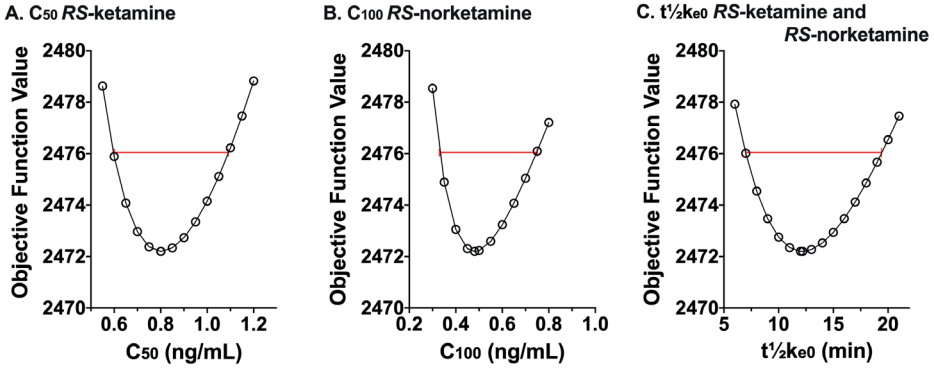

Figure 4. Log likelihood profiles for the C_{50} *RS*-ketamine (**A**), C_{100} *RS*-norketamine (**B**) and $t_{1/2}k_{e0}$ (**C**) parameters. The red bars show the final parameter 95% confidence interval as determined by PsN's "llp" utility.

DISCUSSION

We were unable to reject the Null hypothesis as our results show that *RS*-ketamine and *RS*-norketamine pharmacodynamics (*i.e.* potency and onset/offset times) were similar for endpoints pain pressure threshold and changes in external perception as a measure of ketamine dissociation. Since our results disagree with earlier findings,[6,7] it is important to discuss in detail the different items of our protocol that yielded the current results.

Pain test

We used a manual pressure pain device to detect the pain pressure threshold. Testing was done by a single experienced researcher who displayed a high reproducibility in obtaining the pain threshold response. Still, it may well be that different pain tests give different results with significant differences in pharmacodynamics. For example, in a previous study we tested the effect of the opioid alfentanil on noxious electrical and thermal stimuli and while the potency parameter was similar between tests, the value of the onset/offset parameter, $t_{½}k_{e0}$, differed significantly between tests.[15] We argued at the time that this indicates that the two tests are comparably potent under steady-state conditions but differ in their behavior under dynamic conditions. These differences in dynamic conditions were related to different neuronal circuits activated by the two tests. Hence, the outcome of the study may have been influenced by the choice of pain assay. This not only relates to our study but is equally relevant to other studies. Studying pain relief in chronic (neuropathic) pain patients may overcome this issue.

Dissociation

Dissociation was measured by the *External Perception* questions of the Bowdle questionnaire.[10] This questionnaire was developed in 1998 as a psychological inventory (a hallucinogen rating scale) to quantify ketamine-induced psychedelic symptoms in volunteers and has been used in multiple studies on the effect of various psychedelics on dissociative symptoms. Apart from the *External Perception*, the questionnaire encompasses Internal Perception and Drug High. To test the internal validity of our results, we additionally tested the other two measures of dissociation with similar results as with *External Perception* (data not shown). This indicates that our approach yielded a reliable effect-response relationship. Still, we cannot exclude that other measures of dissociation or other forms of parametrization might have given different results.

Participants

In our study healthy male volunteers were included. We restricted ourselves to a single sex so to prevent noise from possible sex differences. Sex differences have been observed in ketamine pharmacokinetics and pharmacodynamics. [16,17] For example, Morgan et al.[17] showed a greater decrease in cognitive performance in men compared to women following ketamine administration. Further studies are needed to determine the dependency of ketamine endpoints in mixed populations to determine a possible difference between the sexes. Additionally, it may well be that an even better model than the healthy and young volunteer is the patient (of either sex) with acute or chronic pain. Ketamine behavior as an analgesic (*i.e.* reducing existing pain) may well be different from its behavior as an antinociceptive agent (*i.e.* by subduing an experimentally induced pain response) due to differences in activated pain circuits in brain and spinal cord from these two distinct stimuli.

Pharmacodynamic modeling

We successfully modelled the two endpoints simultaneously in our pharmacodynamic analysis. An interesting observation in our data is that PPT and ExP tended to decrease before the *RS*-ketamine infusion ended (Fig. 1). We reasoned that this might be related to the slow but steady increase in concentration of one of ketamine's metabolites. Addition of a norketamine component to the model improved the data fits significantly. This agrees with earlier findings in which norketamine had an antagonistic effect on ketamine-induced pain relief and neurocognitive impairment.[14] Whether this is related to the competition for binding locations on the *N*-methyl-D-aspartate (NMDA) receptor and assuming that norketamine has no inherent efficacy at the receptor, or is related to an effect of norketamine at other receptor systems remain unknown. We tend to the latter hypothesis as studies in rodents show that norketamine has analgesic properties.[18]

The covariate analysis detected no differences between endpoints with respect to potency parameter C50. This indicates that the pain relief and external perception behaved similarly in the steady state. Parameterization of the pharmacodynamic models with distinct C50 values for PPT and ExP gave similar results (data not shown). The values of ketamine C50 depend on the parametrization of the pharmacodynamic models. Apparently, the C50 for ExP matches the C50 for Antinociception, considering the fact that the power function of PPT is an inverse sigmoid.[12] Additionally, the dynamic properties of the PPT and ExP responses were similar with the need for only one parameter for the equilibration between plasma and postulated effect-site concentration (k_{e0}); a model without effect compartment was inferior to the model with just one k_{e0}. Since ketamine displays rapid receptor kinetics,[19] the hysteresis in response ($t_{1/2}k_{e0}$ = 12.2 ± 3.9 min) is best explained by the transfer of ketamine from plasma to its sites of action within the central nervous system and neuronal dynamics.

CONCLUSIONS

We reasoned that similar values for potency (C50 and C100) and $t_{1/2}k_{e0}$ indicate a close and possibly even mechanistic association between endpoints, in agreement with earlier statements that ketamine analgesia is intricately bound to its dissociative effects.[3] Still, this reasoning stands in contrast to earlier observations.[6,7] Gitlin et al.[6] used a statistical approach to show that ketamine and carefully state that ketamine's analgesic effects are not *exclusively* caused by dissociation. Jonkman et al.[7] studied nitric oxide (NO) donation during *S*-ketamine and *RS*-ketamine infusion and concluded that NO depletion following blockade of the NMDA receptor is associated with the psychedelic effects induced by ketamine. The theory behind this observation is that reduced intraneural levels of NO lead to reduction in neuroprotection, neuroplasticity and neurotrophic conditions. Adding NO restores these protective effects and ameliorates psychedelic experience. Interestingly, NO donation had an effect on racemic ketamine but not *S*-ketamine induced psychedelic effect. This suggests that *S*-ketamine induces its psychedelic effect *via* a NO-independent pathway. We did try to unravel the pharmacodynamics of *R*- and *S*-isomers in our study but failed to do so (data not shown). It may well be that the *R*- and *S*-isomers act differently but we could not discriminate between pathways that would suggest dependency or independency between dissociation and analgesia. Such differences may be expected given the different potencies of *R*- and *S*-ketamine in inducing slowing of the electroencephalogram.[20]

Given the complexities of our study and data analysis, *i.e.* complexities related to the pain model, measurement of dissociation, participants and complex modeling of the combination of *RS*-ketamine and *RS*-norketamine, we conclude that although our data

support an intricate association between ketamine analgesia and dissociation, we cannot exclude that some (small) part of the analgesic effects of ketamine is independent from its dissociative effects. In this respect we agree with Gitlin et al.[6]

REFERENCES

1. Kamp J, Van Velzen M, Olofsen E, Boon M, Dahan A, Niesters M: Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature. Expert Opin Drug Metab Toxicol. 2019; 15: 1033-1041
2. Niesters M, Dahan A: Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. Expert Opin Drug Metab Toxicol 2012; 8: 1409-17
3. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, Hurley RW, Viscusi ER, Narouze S, Davis FN, Ritchie EC, Lubenow TR, Hooten WM: Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional Anesthesia and Pain Medicine 2018; 43: 1
4. Oye I: Effects of Ketamine on Sensory Perception: Evidence for a Role of N-Methyl-D-Aspartate Receptors. The journal of pharmacology and experimental therapeutics 1992; 260
5. Brown EN, Purdon PL, Van Dort CJ: General Anesthesia and Altered States of Arousal: A Systems Neuroscience Analysis. Annual Review of Neuroscience 2011; 34: 601-628
6. Gitlin J, Chamadia S, Locascio JJ, Ethridge BR, Pedemonte JC, Hahm EY, Ibala R, Mekonnen J, Colon KM, Qu J, Akeju O: Dissociative and Analgesic Properties of Ketamine Are Independent. Anesthesiology 2020; 133: 1021-1028
7. Jonkman K, van der Schrier R, van Velzen M, Aarts L, Olofsen E, Sarton E, Niesters M, Dahan A: Differential role of nitric oxide in the psychedelic symptoms induced by racemic ketamine and esketamine in human volunteers. Br J Anaesth 2018; 120: 1009-1018
8. Kamp J, Jonkman K, van Velzen M, Aarts L, Niesters M, Dahan A, Olofsen E: Pharmacokinetics of ketamine and its major metabolites norketamine, hydroxynorketamine, and dehydronorketamine: a model-based analysis. Br J Anaesth 2020; 125: 750-761
9. Kamp J, van Velzen M, Aarts L, Niesters M, Dahan A, Olofsen E: Stereoslecetive ketamine effect on cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volinteers. Submitted 2020
10. Bowdle T, Andrew, Radant D, Allen, Cowley S, Deborah, Kharasch D, Evan, Strassman J, Rick, Roy-Byrne P, Peter: Psychedelic Effects of Ketamine in Healthy Volunteers. Anesthesiology 1998; 88: 82-88
11. Rao LK, Flaker AM, Friedel CC, Kharasch ED: Role of Cytochrome P4502B6 Polymorphisms in Ketamine Metabolism and Clearance. Anesthesiology 2016; 125: 1103-1112
12. Sarton E, Olofsen E, Romberg R, Den Hartigh J, Kest B, Nieuwenhuijs D, Burm A, Teppema L, Dahan A: Sex Differences in Morphine Analgesia. Anesthesiology 2000; 93: 1245-1254
13. Beal SL: Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001; 28: 481-504

14. Olofsen E, Noppers I, Niesters M, Kharasch E, Aarts L, Sarton E, Dahan A: Estimation of the contribution of norketamine to ketamine-induced acute pain relief and neurocognitive impairment in healthy volunteers. Anesthesiology 2012; 117: 353-64

15. Olofsen E, Romberg R, Bijl H, Mooren R, Engbers F, Kest B, Dahan A: Alfentanil and Placebo Analgesia. Anesthesiology 2005; 103: 130-139

16. Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E: S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Anesthesiology 2009; 111: 892-903

17. Morgan CJA, Perry EB, Cho H-S, Krystal JH, D'Souza DC: Greater vulnerability to the amnestic effects of ketamine in males. Psychopharmacology 2006; 187: 405-414

18. Holtman Jr JR, Crooks PA, Johnson-Hardy J, Wala EP: Interaction between morphine and norketamine enantiomers in rodent models of nociception. Pharmacology Biochemistry and Behavior 2008; 90: 769-777

19. Shaffer CL, Osgood SM, Smith DL, Liu J, Trapa PE: Enhancing ketamine translational pharmacology via receptor occupancy normalization. Neuropharmacology 2014; 86: 174-180

20. Schuttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB: Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. J Pharmacokinet Biopharm 1987; 15: 241-53