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ANESTHESIOLOGY

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Anesthesiology 2022; 136:792–801

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Ketamine produces potent analgesia and psychedelic effects related to its dissociative properties at subanesthetic doses
- It has been suggested that ketamine analgesia may be generated by its dissociative effects, although there is evidence that suggests the two endpoints are independent and not connected

What This Article Tells Us That Is New

- In a planned secondary analysis, a population pharmacokinetic–pharmacodynamic model of ketamine and its metabolite norketamine was developed to describe the relationship between effect site concentrations of *S*- and *R*-ketamine and their metabolites and pressure pain threshold and the change in external perception as a measure of ketamine psychotropic effect
- The pharmacodynamics of *S*-ketamine did not differ for antinociception and external perception, which had the same potency parameter (C_{50}) and plasma-effect site equilibration half-time whether administered as racemic ketamine or *S*-ketamine
- *R*-ketamine did not contribute to either endpoint, while *S*-norketamine had a small antagonistic effect for both endpoints

ABSTRACT

Background: Ketamine produces potent analgesia combined with psychedelic effects. It has been suggested that these two effects are associated and possibly that analgesia is generated by ketamine-induced dissociation. The authors performed a *post hoc* analysis of previously published data to quantify the pharmacodynamic properties of ketamine-induced antinociception and psychedelic symptoms. The hypothesis was that ketamine pharmacodynamics (*i.e.,* concentration–effect relationship as well as effect onset and offset times) are not different for these two endpoints.

Methods: Seventeen healthy male volunteers received escalating doses of *S*- and racemic ketamine on separate occasions. Before, during, and after ketamine infusion, changes in external perception were measured together with pain pressure threshold. A population pharmacokinetic–pharmacodynamic analysis was performed that took *S*- and *R*-ketamine and *S*- and *R*-norketamine plasma concentrations into account.

Results: The pharmacodynamics of *S*-ketamine did not differ for antinociception and external perception with potency parameter (median [95% CI]) C_{50}, 0.51 (0.38 to 0.66) nmol/ml; blood-effect site equilibration half-life, 8.3 [5.1 to 13.0] min), irrespective of administration form (racemic ketamine or *S*-ketamine). *R*-ketamine did not contribute to either endpoint. For both endpoints, *S*-norketamine had a small antagonistic effect.

Conclusions: The authors conclude that their data support an association or connectivity between ketamine analgesia and dissociation. Given the intricacies of the study related to the pain model, measurement of dissociation, and complex modeling of the combination of ketamine and norketamine, it is the opinion of the authors that further studies are needed to detect functional connectivity between brain areas that produce the different ketamine effects.

(ANESTHESIOLOGY 2022; 136:792–801)

Ketamine is a versatile drug that is used by anesthesiologists, pain physicians, and more recently by psychiatrists.[1] At high doses, ketamine produces a dissociative anesthetic state; 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 can cause misperception of 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

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 675. This article has a visual abstract available in the online version.

Submitted for publication July 1, 2021. Accepted for publication February 15, 2022. Published online first on February 21, 2022. Corrected on May 26, 2022.

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 Anesthesiology 2022; 136:792–801. DOI: 10.1097/ALN.0000000000004176

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 are highly associated and possibly even generated by its dissociative effects.[3–5] This would suggest that the dissociative and analgesic effects of ketamine and its metabolites have common pharmacodynamic properties with a similar potency and onset/offset time. This then suggests that the two endpoints are connected in the sense that brain areas "wire together if they fire together."[6] This is a key concept applied in the analysis of resting state function magnetic resonance imaging data.[7] However, there is also some evidence that suggests that the two endpoints are independent and not connected. For example, in healthy volunteers, Gitlin *et al.*[8] recently studied the effect of ketamine on cuff pain intensity and psychedelic symptoms with and without coadministration 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 a NO donor, sodium nitroprusside, modestly reduced psychedelic symptoms in volunteers receiving racemic ketamine but not in those receiving *S*-ketamine.[9] Such an effect was not observed for ketamine analgesia (A. Dahan, M.D., Ph.D., unpublished data, digital communication March 4, 2022). To determine whether ketamine-induced dissociation and analgesic behavior are connected, we performed a population pharmacokinetic–pharmacodynamic analysis in healthy volunteers. All subjects received increasing doses of racemic ketamine and *S*-ketamine on different occasions, and were tested concomitantly for pain relief to a pressure pain stimulus and alterations in perception of external stimuli as a measure of psychedelic effect. We chose to analyze the perception of external stimuli as we argued that internal perception could be influenced by the imposed painful stimuli. Our null hypothesis was that ketamine pharmacodynamics (*i.e.,* concentration–effect relationship, as well as times for onset and offset of effect) are not different for these two endpoints, an indication that dissociation and analgesia from ketamine are interconnectedly generated in the brain.

Materials and Methods

Ethics and Subjects

The data used in this analysis are part of a larger data set that was used previously to study the effects of sodium nitroprusside on ketamine-induced adverse effects,[9] and to construct a population pharmacokinetic model of ketamine and its metabolites,[10] as well as a pharmacodynamic model of ketamine-induced changes in cardiac output.[11] In the secondary analysis that is currently planned, we developed a population pharmacokinetic–pharmacodynamic model of ketamine and its metabolite norketamine to describe the relationship between plasma concentrations of *S*- and *R*-ketamine (and their metabolites) and pressure pain threshold and the change in external perception as a measure of ketamine psychotropic effect. The study protocol was approved by the Institutional Review Board (Medical Ethics Review Committee Leiden, Den Haag, Delft, Leiden University Medical Center, Leiden, The Netherlands) and registered at the trial register of the Dutch Cochrane Center (www.trialregister.nl) under registration No. 5359 (principal investigator: A. Dahan; registration date, August 11, 2015). The study was performed in 20 healthy male volunteers (age, 18 to 34 yr; body mass index, 20 to 30 kg/m^2). All subjects gave written informed consent before participation in the study. Specific inclusion and exclusion criteria are found in Jonkman *et al.*[9]

Study Design

The original study was a four-arm, randomized, double-blind crossover study during which *S*-ketamine or racemic ketamine was infused against a background of either sodium nitroprusside or normal saline (placebo). For the current analysis, we used the data obtained on two occasions in which subjects received escalating intravenous doses of *S*-ketamine (Ketanest-S, Eurocept BV, The Netherlands) or racemic ketamine (Ketalar, Pfizer, Germany) during a period of 3 h. *S*-ketamine doses were 0.14 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 h, then 0.28 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 h, and finally 0.57 $mg \cdot kg^{-1} \cdot h^{-1}$ for the last 1-h period. The equivalent administered racemic ketamine doses were as follows: first hour, 0.28 mg/kg; second hour, 0.57 mg/kg; and third hour, 1.14 mg/kg. All infusions were against a background of normal saline infusion.

Data Collection

Data were collected before and during both the racemic ketamine and S-ketamine infusions.

Pain Pressure Threshold. The pain pressure threshold was measured by applying an increasing pressure to a 1-cm^2 skin area between the thumb and index finger, using the FP 100 N Algometer (FDN 100, Wagner Instruments Inc., 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 the start of the racemic ketamine infusion (baseline), followed by measurements at 15-min intervals during and after racemic ketamine infusion. Measurements continued until 2 h after termination of the racemic ketamine infusion.

Bowdle Questionnaire. External perception was obtained from the Bowdle questionnaire.[12] 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 analog scale that ranges from "not at all" to "extreme." External perception relates to the misapprehension of external stimuli

or 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 colors changed"; and "The intensity of sound changed." External perception was measured at time = 0 (baseline) and 20, 40, 55, 80, 100, 115, 140, 160, 175, 200, 220, 240, 260, and 280 min after the start of ketamine infusion.

Plasma Concentrations: R-*and* S-*ketamine,* R-*and* S-*norketamine.* *R*- and *S*-dehydronorketamine and total hydroxynorketamine were not considered in the current analysis. At regular time points (time = 0 [baseline] and time = 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 concentrations were measured in the laboratory of Evan Kharasch, M.D., Ph.D., at Washington University School of Medicine, St. Louis, Missouri, as described by Rao *et al.*, by enantioselective high-performance liquid chromatography–tandem mass spectrometry after solid-phase extraction.[13]

Data Analysis

The pharmacokinetic data were analyzed separately in NONMEM (ICON Development Solution, USA) and previously reported.[10] The pharmacokinetic data were analyzed with a two-compartment ketamine, two-compartment norketamine, one-compartment dehydronorketamine, and two-compartment hydroxynorketamine model. In between the central ketamine and norketamine compartments, two metabolism or delay compartments were included (see fig. 2 in Kamp *et al.*[10]). In this study, we use the measured *R*- and *S*-ketamine and norketamine plasma concentration data. From the earlier model, empirical Bayesian estimates of the pharmacokinetics parameters were obtained, and their fixed values were used as input to the pharmacodynamic model.

To account for a possible delay between plasma concentrations and effect, effect compartments for *S*- and *R*-ketamine and *S*- and *R*-norketamine were postulated that were assumed to equilibrate with the central compartment with an effect half-time of $t_{½} = \ln(2)/k_{e0}$, where k_{e0} is a rate constant.

For the two endpoints, pressure pain threshold and external perception, and the two compounds, *S*- and racemic ketamine, four initial pharmacodynamic models were built and next combined, by testing if typical parameter values and their interindividual variances could be set to the same value. We focus on the final model, but show how the objective function values and 95% CI of the parameter estimates change with changing assumptions.

Pressure pain was modeled as follows:

$$PTT(t) = BLN \times \left(1 + C_k(t)^{\gamma}\right) \text{and } C_K(t) = \left(\frac{C_R(t)}{C_{50R}}\right) + \left(\frac{C_S(t)}{C_{50S}}\right) \quad (1)$$

where $PPT(t)$ is the amount of pressure in newtons applied at which the subjects first reported pain at time t, BLN is the estimated pressure pain threshold at baseline, $C_R(t)$ and $C_S(t)$ are the effect-site concentration of *S*- and *R*-ketamine in nanomoles per milliliter at time t, C_{50R} and C_{50S} are the estimated *S*- and *R*-ketamine effect-site concentrations needed to increase the pain pressure threshold by 100% (in nanomoles per milliliter),[14] and γ is the Hill coefficient.

External perception was described by a sigmoid E_{max} model:

$$ExP(t) = E_{max} \times \left(\frac{C_k(t)^{\gamma}}{1 + C_k(t)^{\gamma}}\right) \text{and}$$
$$C_K(t) = \left(\frac{C_R(t)}{C_{50R}}\right) + \left(\frac{C_S(t)}{C_{50S}}\right) \quad (2)$$

where $ExP(t)$ is the experienced level of external perception as rated on a 100-mm visual analog scale at time t, E_{max} is the maximum effect on external perception (100), $C_R(t)$ and $C_S(t)$ are the effect-site concentration of *S*- and *R*-ketamine in nanomoles per milliliter at time t, C_{50R} and C_{50S} are the *R*- and *S*-ketamine effect-site concentration in nanomoles per milliliter needed to reach 50% of E_{max} of external perception, and γ is the Hill coefficient. Since external perception was measured on a 100-mm visual analog scale, ratings could not be more than 100 points.

Since we observed a small discrepancy in the individual model fits for external perception and to a lesser extent for pain pressure threshold during the infusion phase, we postulated that a norketamine effect might be present. We therefore added *S*- and *R*-norketamine as input to the models, based on a receptor kinetics approach, in which *S*- and *R*-norketamine could displace *S*- and *R*-ketamine from the receptor. The consequence of this would be a counteracting effect of *S*- or *R*-norketamine on the effects of *S*- and *R*-ketamine.[15] The effects of *S*- and/or *R*-norketamine were defined as follows:

$$EFF_{NK}(t) = \frac{C_{NK}(t)}{C_{100NK}} \quad (3)$$

where $C_{NK}(t)$ is the *S*- or *R*-norketamine plasma concentration in nanomoles per milliliter, and C_{100NK} is the *S*- or *R*-norketamine effect-site concentration causing a 100% increase in C_{50K}. So, in equations 1 and 2, C_{50R} and C_{50S} were replaced by the following:

$$C_{50KN}(t) = C_{50x} \times [1 + EFF_{NK}(t)] \quad (4)$$

where x is either *S*- or *R*-ketamine and C_{50KN} the plasma ketamine concentration needed to increase the pain pressure threshold by 100% for pressure pain and reach 50%

of E_{max} for external perception considering a counteracting effect of *S*- or *R*-norketamine on the effects of *S*- and *R*-ketamine.

Statistical Analysis

Data analysis was performed using NONMEM version 7.5.0 with *P* values less than 0.01 considered significant. 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 is the population parameter, and η_i is the random difference between the population and individual parameters, where its variance is the sum of interoccasion (ν^2) and interindividual variability (ω^2). In addition to the $COV step in NONMEM to determine the standard error of the (parameter) estimate, Perl-speaks-NONMEM's log likelihood profiling (llp) utility was used to determine the 95% CI for parameters *S*- and/or *R*-ketamine C_{50}, *S*- and/or *R*-norketamine C_{100}, and $t_{½}k_{e0}$. *P* values less than 0.01 were considered significant.

We did not perform an *a priori* sample size analysis as this was a secondary analysis from existing data. We did earlier perform a sample size analysis based on this data set and calculated an effect size of 20% as clinically relevant and concluded that 17 subjects were necessary to detect a difference between single-treatment arms at $P < 0.05$ and $1 - \beta > 0.80$.[9] This would translate into a 20% difference in C_{50} values between endpoints in the current analysis as a clinically relevant endpoint in our population of 17 subjects. The current data set is larger than the set used for sample size analysis (one arm of the study) and consists of a comparison of endpoints using data derived from two study arms (one treated with *S*-ketamine and the other with racemic ketamine). We therefore assume to have sufficient power to detect a difference in C_{50} values between endpoints.

Results

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

We tested various pharmacodynamic models, with separate analyses of external perception *versus* pressure pain threshold, and separate analyses of *S*-ketamine *versus* racemic ketamine, and tested whether the parameter values and their interindividual variances could be set at equal values. The objective function values of the models and the 95% CI of the parameter estimates are given in fig. 1 and table 1. They show the large overlap of 95% CI of the parameter estimates when analyzed separately, and the improvement in objective function in the final model that combined the two endpoints and the two formulations into one model. An important observation was that adding *R*-ketamine or its metabolite *R*-norketamine did not cause a significant improvement of any of the models, and these were therefore not incorporated (*i.e.,* values for *R*-ketamine and *R*-norketamine C_{50} were disproportionally high, without a significant decrease in NONMEM's objective function value). Our analyses indicate that the final model is one with similar pharmacodynamic parameter estimates for the two endpoints, irrespective of formulation. Moreover, in the analyses, we tested whether a model that included *S*-norketamine would improve the objective function values. It did so for the final model by 373 points. Finally, for the two endpoints and two formulations, no differences in k_{e0} could be detected.

Plots showing the population predicted pharmacodynamic outcomes and the observed data points for each individual *versus* time are given in fig. 2. Goodness-of-fit plots are given in fig. 3 (observed *vs.* individual predicted; observed *vs.* population predicted; individual weighted residual *vs.* time; normalized prediction discrepancy error *vs.* time; and conditioned weighted residuals *vs.* population predicted) for the two endpoints, and the two formulations; visual predictive checks are given in fig. 4. All indicate that the final model adequately describes the data from both endpoints. Estimated pharmacodynamic parameter estimates are given in table 2 (estimate ± standard error of the estimate): C_{50} *S*-ketamine, 0.51 ± 0.12 nmol/ml; C_{100} *S*-norketamine, 0.34 ± 0.13 nmol/ml; and $t_{½}k_{e0}$, 8.3 ± 3.4 min. Log likelihood profiles (fig. 5) for parameters *S*-ketamine C_{50}, *S*-norketamine C_{100}, and $t_{½}k_{e0}$, showed 95% CI of 0.39 to 0.66 nmol/ml, 0.23 to 0.53 nmol/ml, and 5.1 to 12.6 min, respectively.

Interoccasion variance was not estimable for the baseline of the pressure pain threshold, whereas interindividual variability was not estimable for the remaining parameters. The interindividual and interoccasion variances may not both be identifiable from variable pharmacodynamic (and indeed also often with usually less variable pharmacokinetic) data with a limited number of subjects. Therefore, the total variance may be attributed to the component that has the largest estimation precision, which does not imply that the other component has no variability. Apparently, the interindividual variability of the baseline of the pressure pain threshold had larger estimation precision than its interoccasion variability, and the reverse was true for the remaining parameters.

Discussion

We were unable to detect a difference in the *S*-ketamine and *S*-norketamine pharmacodynamic model parameters (*i.e.,* potency and onset/offset times) for endpoints pain pressure threshold and changes in external perception, as

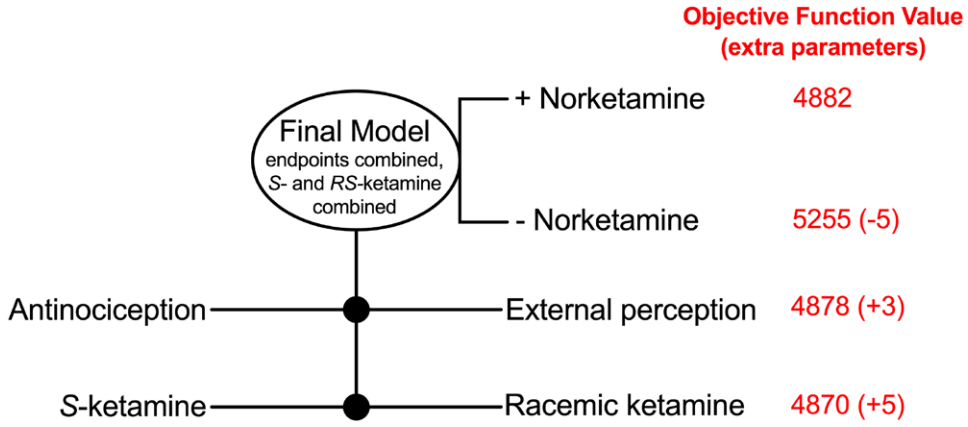

Fig. 1. Objective function values of the different models used to model the effect of *S*-ketamine and/or racemic ketamine on pain pressure threshold and/or external perception. The objective function values are given with the additional model parameters for each step in brackets.

Table 1. 95% Confidence Intervals

		Models with the Two Endpoints Analyzed Separately		Models with the Two Administration Forms Analyzed Separately	
	Final Model	Pain Pressure Threshold	External Perception	*S*-ketamine	Racemic Ketamine
C_{50S} ketamine, nmol/ml	0.38–0.66	0.40–0.81	0.34–0.58	0.35–0.76	0.35–0.60
C_{100S} norketamine, nmol/ml	0.23–0.53	0.21–0.63	0.22–0.49	0.18–0.52	0.22–0.55
$t_{½}k_{e0}$, min	5.1–13.0	5.0–16.0	5.0–13.0	4.0–17.0	4.6–13.0

R-ketamine did not contribute to the pain pressure response or to external perception.

C_{50S} ketamine, *S*-ketamine concentrations causing a 100% increase in pain pressure threshold or causing half-maximum effect in external perception; C_{100S} norketamine, *S*-norketamine concentration causing a 100% increase in C_{50} of *S*-ketamine; $t_{½}k_{e0}$, blood-effect compartment equilibrium half-life for both ketamine and norketamine.

a measure of ketamine dissociation, irrespective of administered formulation (*S*-ketamine or racemic ketamine). Additionally, we observed that *R*-ketamine did not contribute to the measured effects after racemic ketamine administration. Since our results disagree with earlier findings,[8,9] 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, $t½k_{e0}$, differed significantly between tests.[16] 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. Note further that cold pressor pain and cuff pain require many minutes to complete, which may affect the values of k_{e0} and C_{50}. Pressure pain (and also thermal and electrical pain) require a few seconds to complete.

Dissociation

Dissociation was measured by the external perception questions of the Bowdle questionnaire.[12] This questionnaire was developed in 1998 as a psychologic 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

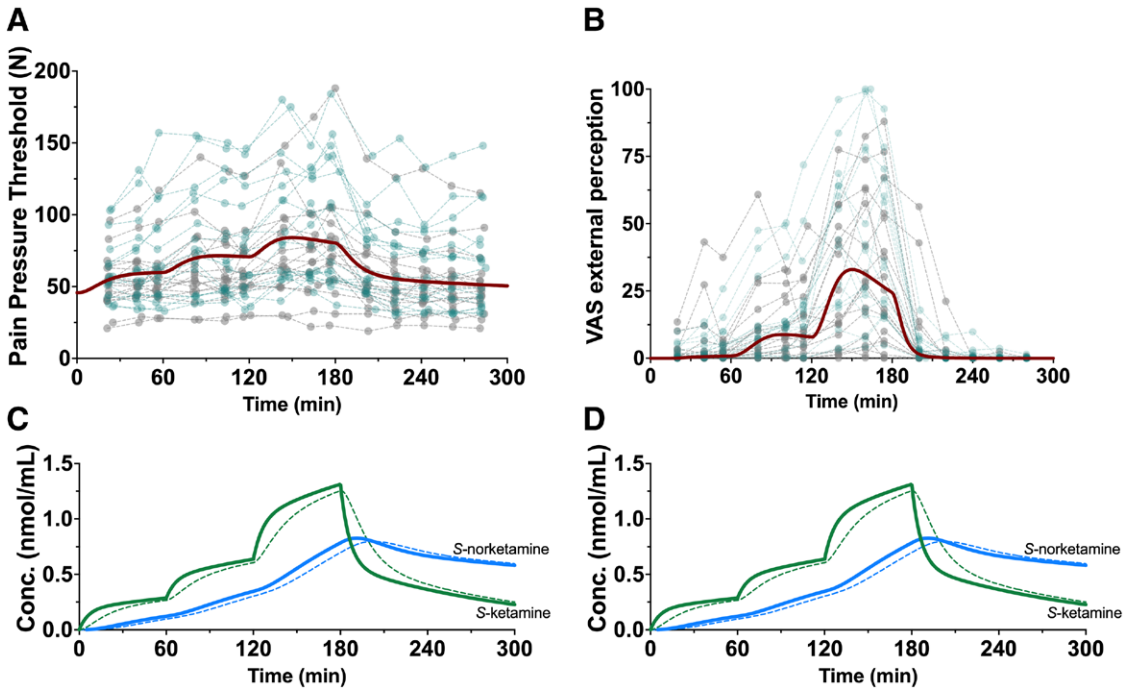

Fig. 2. Plots showing the population predicted pharmacodynamic outcomes (*red lines*) and the observed data points for each individual *versus* time (*gray dots* for *S*-ketamine, *green dots* for racemic ketamine formulations). (*A*) Plot showing pressure pain data and population predicted values and (*B*) plot showing external perception data and population predicted values. *C* and *D* show the *S*-ketamine (*green line*) and *S*-norketamine (*blue line*) plasma concentration–time profiles and corresponding estimated effect-site concentrations (*broken green line* for *S*-ketamine and *broken blue line* for *S*-norketamine). VAS, visual analog scale.

symptoms. Apart from external perception, the questionnaire encompasses internal perception and drug high. To test the internal validity of our results, we additionally tested these 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 to reduce variability 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 with women after ketamine administration. Further studies are needed to determine the connectivity of ketamine endpoints in mixed populations to determine a possible difference between the sexes. Additionally, it may well be that a model with better applicability 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 modeled the two endpoints simultaneously in our pharmacodynamic analysis. An interesting observation in our data is that pressure pain threshold and external perception tended to decrease before the ketamine infusion ended (fig. 2). 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.[15] Whether this is related to the adaptation of the pain system (which we cannot test as we did not include a placebo arm), due the competition for binding locations on the *N*-methyl-D-aspartate receptor and assuming that norketamine has no inherent efficacy at the receptor, or is related to an effect of norketamine at other receptor

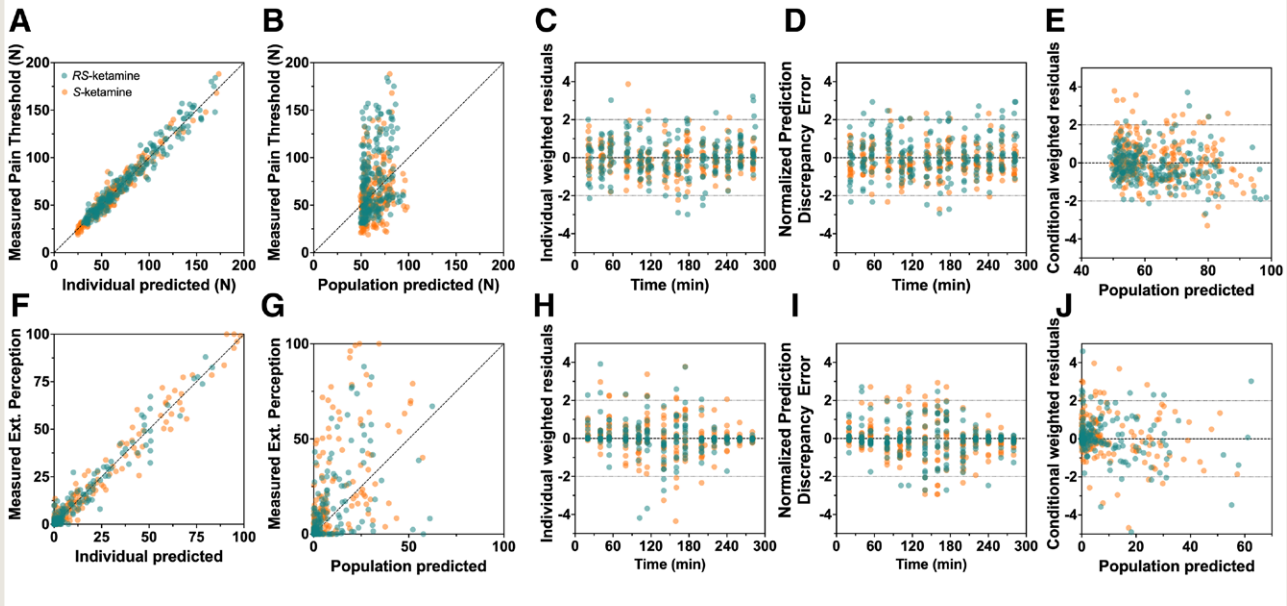

Fig. 3. Goodness-of-fit plots for the population pharmacodynamic model: pain pressure threshold (*A* to *E*) and external perception (*F* to *J*). (*A*) Observed *versus* individual predicted. (*B*) Observed pain pressure threshold *versus* population predicted pain pressure threshold. (*C*) Individual weighted residual *versus* time. (*D*) Normalized prediction discrepancy error *versus* time. (*E*) Conditioned weighted residuals *versus* population predicted. (*F*) Observed *versus* individual predicted. (*G*) Observed *versus* population predicted. (*H*) Individual weighted residual *versus* time. (*I*) Normalized prediction discrepancy error *versus* time. (*J*) Conditioned weighted residuals *versus* population predicted.

systems, remains unknown. The former hypothesis stands in contrast with studies in rodents showing that norketamine has analgesic properties.[18]

We detected no differences between endpoints with respect to potency parameter C_{50}. This indicates that the pain relief and external perception behaved similarly in the steady state. Parameterization of the pharmacodynamic models with distinct C_{50} values for pain pressure threshold and external perception gave similar results (table 1). The values of ketamine C_{50} depend on the parametrization of the pharmacodynamic models. Apparently, the C_{50} for external perception matches the C_{50} for antinociception, considering the fact that the power function of pain pressure threshold is an inverse sigmoid.[14] Additionally, the dynamic properties of the pain pressure threshold and external perception responses were similar with the need for only one

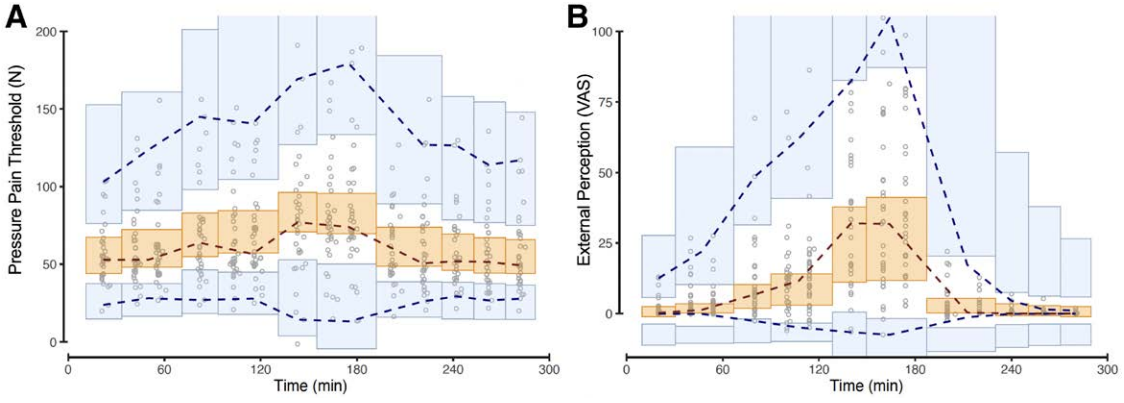

Fig. 4. Visual predictive checks for the pressure pain threshold (*A*) and external perception (*B*) data. The middle *dotted line* represents the 50th percentile of the observed data. The upper and lower *broken lines* show the 5th and 95th percentiles of the observed data, respectively. The 95% CI of the 50th percentile of the simulated data is given by the *orange shaded area*. The upper and lower *gray/blue shaded areas* represent the 95% CI of the 5th and 95th percentile of the simulated data. VAS, visual analog scale.

Table 2. Population Pharmacodynamic Parameter Values of the Final Pharmacokinetic–Pharmacodynamic Model

	Typical Parameter Value ± Standard Error of the Estimate	Interoccasion Variances (v^2) ± Standard Error of the Estimate	Interindividual Variances (ω^2) ± Standard Error of the Estimate
Baseline pressure pain threshold, N	45.7 ± 4.2	—	0.18 ± 0.05
E_{MAX} external perception, mm	100 (FIXED)*	0.44 ± 0.32	—
Shape parameter (GAMMA) pain threshold	1.31 ± 0.41	0.28 ± 0.12	—
Shape parameter (GAMMA) external perception	5.33 ± 1.23	—	—
C_{50S} ketamine, nmol/ml	0.51 ± 0.12	0.16 ± 0.09	—
C_{100S} norketamine, nmol/ml	0.34 ± 0.13	0.37 ± 0.29	—
$t_{½}k_{e0}$, min	8.3 ± 3.4	0.39 ± 0.16	—
Additive error pressure pain threshold (σ^2), N^2	54 ± 10.1		
Additive error external perception (σ^2), mm^2	19.2 ± 5.1		

*Parameter fixed to 100. —Dash indicates parameters not included in the statistical model

C_{50S} ketamine, *S*-ketamine concentrations causing a 100% increase in pain pressure threshold or causing half-maximum effect in external perception; C_{100S} norketamine, *S*-norketamine concentration causing a 100% increase in C_{50S} of ketamine; E_{MAX}, external perception is the maximum possible effect of external perception; $t_{½}k_{e0}$, blood-effect compartment equilibrium half-life for both ketamine and norketamine.

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 is best explained by the transfer of ketamine from plasma to its sites of action within the central nervous system and neuronal dynamics.

We did not detect a contributing effect of the *R*-ketamine isomer to either pain relief or dissociation. An absence of an *R*-ketamine effect was observed for cardiac output and further agrees with earlier observations.[11] For example, at anesthetic doses, blood pressure effects of *S*-ketamine exceed those of racemic ketamine,[20] and *S*-ketamine produces a greater reduction of the electroencephalogram power spectrum compared to either *R*- or racemic ketamine.[21] At subanesthetic doses, the analgesic *S*-ketamine:racemic ketamine potency is about 2,[9] indicative of a lack of efficacy of *R*-ketamine in producing pain relief. These data contrast with the observation that particularly *R*-ketamine produces potent antidepression, at least in animal models.[22,23]

Comparison with the Literature

We reasoned that similar values for potency (C_{50} and C_{100}) and $t_{1/2}k_{e0}$ indicate a close, possibly even mechanistic, connectivity 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 from Gitlin *et al.*,[8] Hahm *et al.*,[24] and Jonkman *et al.*[9]

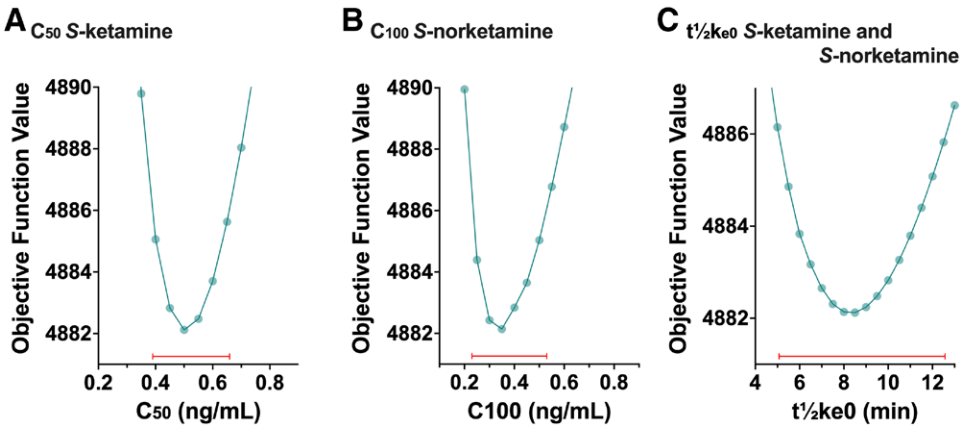

Fig. 5. Log likelihood profiles for C_{50} *S*-ketamine (*A*), C_{100} *S*-norketamine (*B*), and $t_{1/2}k_{e0}$ (*C*) parameters. The *red line* shows the final parameter 95% CI as determined by Perl speaks NONMEM, "llp" utility. C_{50} *S*-ketamine, estimated *S*-ketamine effect-site concentration needed to increase the pain pressure threshold by 100%; C_{100} *S*-norketamine, effect-site *S*-norketamine concentration causing a 100% increase in C_{50} *S*-ketamine; $t_{1/2}k_{e0}$, *S*-ketamine and *S*-norketamine blood-effect site equilibration half-life.

Gitlin *et al.*[8] and Hahm *et al.*[24] used a statistical approach to show that racemic ketamine analgesic and dissociative effects are not correlated. They studied racemic ketamine effect with and without one bolus dose of midazolam and with and without sevoflurane anesthesia, and state that ketamine's analgesic effects are not *exclusively* caused by dissociation. However, in contrast to our study, Gitlin *et al.*[8] and Hahm *et al.*[24] used supra-analgesic doses of intravenous racemic ketamine (140 mg in their average 70-kg subject) far greater than the advocated dose for analgesia. Additionally, they did not measure plasma ketamine or norketamine concentrations and therefore were not aware of the pharmacokinetic–pharmacodynamic relationship under control conditions or conditions in which racemic ketamine was combined with either midazolam or sevoflurane. Both pharmacokinetic and pharmacodynamic interactions may have influenced the outcome of the studies of Gitlin *et al.*[8] and Hahm *et al.*[24] Furthermore, in contrast to our approach with mechanistic and data-rich analyses, Gitlin *et al.*[8] analyzed their data using a time-squared function (parabola), which has no mechanistic meaning. Finally, to attenuate dissociation, they gave 2 mg midazolam, which is insufficient to tame the dissociation from 140 mg ketamine. We argue that a better approach would have been to administer a continuous midazolam infusion rather than one low-dose midazolam bolus.

Jonkman *et al.*[9] studied NO donation during *S*-ketamine and racemic ketamine infusion and concluded that NO depletion after blockade of the *N*-methyl-D-aspartate 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.

Limitations and Future Perspectives

We have discussed the different components of our study that may have influenced the outcome of our study. One important further limitation is that, while this was a planned secondary analysis, the initial setup of the study was not aimed at finding a difference in the pharmacodynamics between endpoints. Hence, further studies are needed to definitely determine the link between dissociation and pain relief, and possibly also other outcomes such as antidepression induced by ketamine. It is possible that functional magnetic resonance imaging studies may provide more definitive answers.

Conclusions

Intuitively, a dissociation between the thalamus and limbic system, resulting from the dissociative state induced by ketamine, seems mechanistically well able to subdue the perception of pain and increase satisfaction with pain relief. We tested this assumption by performing a secondary preplanned analysis of an information-rich data set and compared the pharmacodynamics of two ketamine endpoints: antinociception and changes in the perception of external stimuli using state-of-the-art modeling analyses in NONMEM. We conclude that our data support an association or connectivity between ketamine analgesia and dissociation. Further studies are needed to definitely detect functional connectivity and possibly even dependency between brain areas that produce the different ketamine effects.

Research Support

Support was provided from institutional and/or departmental sources. This work is part of the TAPTOE (Tackling and Preventing the Opioid Epidemic) research project. This research received funding from the Dutch Research Council (The Hague, The Netherlands) in the framework of the NWA-ORC (Netherlands Science Agenda - Research On Routes by Consortia) Call (NWA.1160.18.300).

Competing Interests

The Anesthesia and Pain Research Unit of the Department of Anesthesiology, Leiden University Medical Center (Leiden, The Netherlands), received/receives funding from AMO Pharma Ltd. (Leeds, United Kingdom), Bedrocan BV (Veendam, The Netherlands), Grünenthal GmbH (Aachen, Germany), Medasense Biometrics Ltd. (Ramat Gan, Israel), Medtronic (Minneapolis, Minnesota), MSD Nederland BV (Haarlem, The Netherlands), LTS Lohmann Therapie Systeme AG (Andernach, Germany), and Trevena Inc. (Chesterbrook, Pennsylvania). Dr. Dahan received consultancy and/or speaker fees from Enalare Therapeutics Inc. (Princeton, New Jersey), Grünenthal BV (Woerden, The Netherlands), Medasense Biometrics Ltd. (Ramat Gan, Israel), Trevena Inc., and MSD Nederland BV and received grants/awards from ZonMW (The Hague, The Netherlands) and the U.S. Food and Drug Administration (Silver Spring, Maryland).

Reproducible Science

Full protocol available at: a.dahan@lumc.nl. Raw data available at: a.dahan@lumc.nl.

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