Anesthesiology 2009; 111:892–903

S(+)-ketamine Effect on Experimental Pain and Cardiac Output

A Population Pharmacokinetic-Pharmacodynamic Modeling Study in Healthy Volunteers

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Background: **Low-dose ketamine behaves as an analgesic in the treatment of acute and chronic pain. To further understand ketamine's therapeutic profile, the authors performed a population pharmacokinetic-pharmacodynamic analysis of the S(+)-ketamine analgesic and nonanalgesic effects in healthy volunteers.**

Methods: **Ten men and ten women received a 2-h S(+)-ketamine infusion. The infusion was increased at 40 ng/ml per 15 min to reach a maximum of 320 ng/ml. The following measurements were made: arterial plasma S(+)-ketamine and S(+)-norketamine concentrations, heat pain intensity, electrical pain tolerance, drug high, and cardiac output. The data were modeled by using sigmoid Emax models of S(+)-ketamine concentration *versus* effect and S(+)-ketamine + S(+)-norketamine concentrations *versus* effect.**

Results: **Sex differences observed were restricted to pharmacokinetic model parameters, with a 20% greater elimination clearance of S(+)-ketamine and S(+)-norketamine in women resulting in higher drug plasma concentrations in men. S(+)-ketamine produced profound drug high and analgesia with six times greater potency in the heat pain than the electrical pain test. After ketamine-infusion, analgesia rapidly dissipated; in the heat pain test but not the electrical pain test, analgesia was followed by a period of hyperalgesia. Over the dose range tested, ketamine produced a 40–50% increase in cardiac output. A significant consistent contribution of S(+)-norketamine to overall effect was detected for none of the outcome parameters.**

Conclusions: **S(+)-ketamine displays clinically relevant sex differences in its pharmacokinetics. It is a potent analgesic at already low plasma concentrations, but it is associated with intense side effects.**

KETAMINE is a phenylcyclidine derivative introduced in the early 1960s as an intravenous anesthetic agent. Ketamine acts as a noncompetitive antagonist of the ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptor.[1] Low-dose or subanesthetic ketamine behaves as an analgesic in the treatment of acute (postoperative) pain and chronic pain associated with peripheral and central sensitization.[2] Clinical studies on the efficacy of low-dose ketamine in the treatment of acute pain indicate that it enhances opioid-induced acute antinociception and consequently reduces opioid consumption.[3–5] Few studies have addressed the inherent analgesic properties of ketamine in humans in acute pain models. The available studies indicate that low-dose ketamine produces dose-dependent attenuation of pain intensity and pain unpleasantness (*i.e.*, the affective pain component) by using noxious stimulation with heat and cold pain stimuli.[6–9] In the current study, we performed a population pharmacokinetic-pharmacodynamic (PK-PD) analysis of the antinociceptive properties (using cutaneous noxious heat and electrical pain models) and side effects (drug high and increase in cardiac output) of the S(+)-enantiomer of ketamine in healthy male and female volunteers. We chose to study the S(+)-enantiomer of ketamine as it is currently available in an increasing number of countries and displays greater analgesic potency than either the racemic mixture or R(–)-ketamine, with possibly fewer side effects than the racemic mixture.[10] The focus of our study is on the possible existence of sex differences in ketamine's pharmacokinetics and/or pharmacodynamics, contribution of norketamine to ketamine effect, and the comparison of ketamine's potency with respect to different measured endpoints.

Materials and Methods

Subjects

Twenty healthy volunteers (10 men and 10 women; age 18–30 yr; body mass index less than 28 kg/m^2) were recruited to participate in the study after approval of the protocol (trial register #NTR696, ISRCTN 2052216) by the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). Written and oral informed consent was obtained before inclusion in the study. All females were taking oral contraceptives; all subjects were instructed not to eat or drink for at least 6 h before the study.

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Received from the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands. Submitted for publication November 26, 2008. Accepted for publication June 18, 2009. Supported in part by TREND (Trauma RElated Neuronal Dysfunction), a nonprofit consortium of academic hospitals, technical research groups, and companies focused on the study of complex regional pain syndrome type 1 (Delft, The Netherlands).

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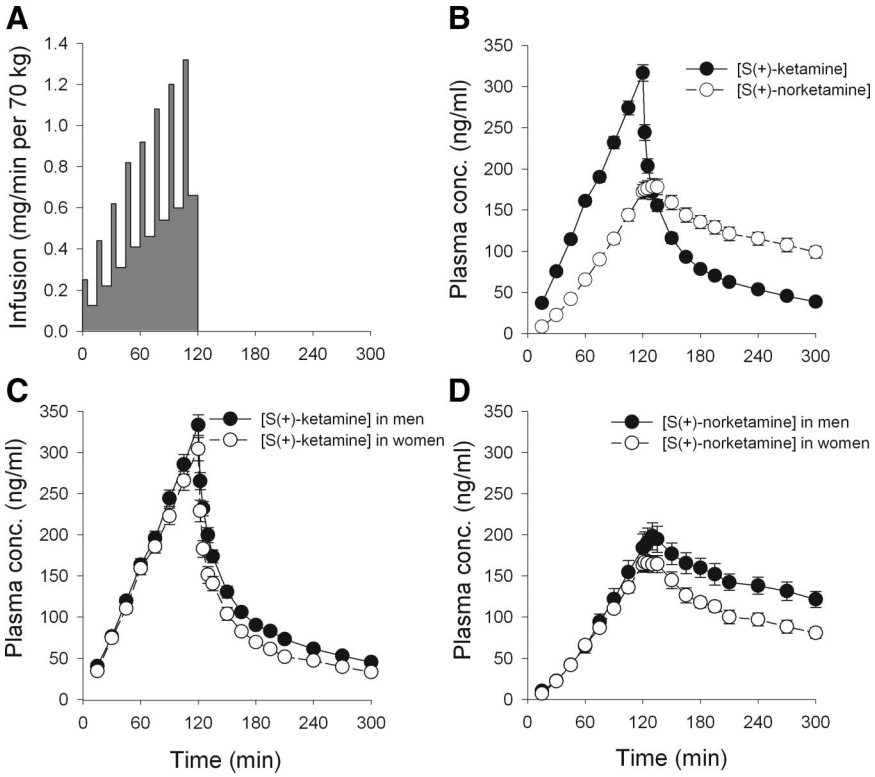

Fig. 1. (*A*) S(+)-ketamine infusion scheme in mg/min per 70 kg. During the 120 min infusion time, 66.5 mg S(+)-ketamine was infused in a 70-kg volunteer. (*B*) Plasma concentrations of S(+)-ketamine and S(+)-desmethyl-ketamine (= S(+)-norketamine). Mean values derived from all subjects (*n* = 20, 10 men/10 women). (*C*) Plasma S(+)-ketamine concentrations in men *versus* women. (*D*) Plasma S(+)-norketamine concentrations in men *versus* women. Values are mean ± SEM.

Study Design: S(+)-ketamine Infusion and Blood Sampling

After arrival in the research unit, an arterial line for blood sampling and cardiac output measurement was placed in the left or right radial artery. In the contralateral arm an intravenous line was inserted for drug infusion. Total study duration was 5 h, of which S(+)-ketamine was administered during the first 2 h. An infusion scheme was designed to create an increase in S(+)-ketamine concentration of 40 ng/ml per 15 min. To do so, the infusion scheme was as follows (all doses are per 70 kg; see fig. 1A): min 0–5, 1.25 mg (given in 5 min); min 5–15, 1.25 mg (given in 10 min); min 15–20, 2.2 mg; min 20–30, 2.2 mg; min 30–35, 3.1 mg; min 35–45, 3.1 mg; min 45–50, 4.1 mg; min 50–60, 4.1 mg; min 60–65, 4.6 mg; min 65–75, 4.6 mg; min 75–80, 5.4 mg; min 80–90, 5.4 mg; min 90–95, 6.0 mg; min 95–105, 6.0 mg; min 105–110, 6.6 mg; min 110–120, 6.6 mg. Arterial blood sampling was performed before any drug infusion (1 sample), during drug infusion just before each increase in infusion rate (8 samples), and at times t = 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, and 180 min after the end of drug infusion. Plasma was separated within 15 min of blood collection and stored at –25°C until analysis. For the analysis of S(+)-ketamine and its main metabolite S(+)-norketamine, see appendix 1.

Pharmacodynamic Endpoints

Heat Pain. Noxious thermal stimulation was induced using the TSA-II device (Medoc Ltd., Ramat Yishai, Israel). Using a 3 × 3–cm thermode, the skin on the volar side of the left or right forearm was stimulated with a gradually increasing stimulus (0.5°C/s, baseline temperature 32°C). The peak temperature depended on the outcome of a set of tryout stimuli. The subjects rated the pain to three peak temperatures: 46°C, 48°C, and 49°C. The lowest stimulus causing a visual analogue score (VAS) greater than 6 was used in the study. The tryout data were discarded. Next baseline values (*i.e.*, predrug VAS) were obtained. The volar part of the arm was divided into six zones and marked as previously described.[11] The thermode was moved from zone to zone between stimuli. After each heat stimulus, the subjects rated pain intensity and pain unpleasantness by using a 10-cm visual analogue score ranging from 0 (no pain) to 10 (most intense pain of most unpleasant pain experience).

Electrical Pain. Transcutaneous electrical stimulation was applied to the skin overlying the tibial bone of the left leg *via* two surface electrodes. The electrodes were attached to a current stimulator (Leiden University Medical Center, Leiden, The Netherlands).[11] The intensity of the noxious stimulation was increased from 0 mA in steps of 0.5 mA/s (pulse duration 0.2 ms, 10 Hz, cutoff 128 mA). The subjects pressed a button on a control box when the stimulus became painful (pain threshold) and a second button when no further increase in stimulus intensity was acceptable (pain tolerance). Pressing the second button ended the stimulus train. The currents of pain threshold and tolerance were stored for further analysis. After a training session, baseline values were obtained in triplicate; the average values were used in the data analysis.

Pain measurements were performed at times t = 0 (baseline), 12, 27, 42, 57, 72, 87, 102, and 117 min during drug infusion, and at t = 12, 27, 42, 57, 72, 87, 117, 147, and 177 min after termination of the infusion. Heat pain assessment preceded electrical pain testing.

Drug High and Cardiac Output (CO). At regular intervals, the subjects rated the feeling of drug high (drug-induced euphoria) on a 10-cm paper scale ranging from 0 (absence of high) to 10 (maximal high rating). Times of measurement are: t = 0 (baseline), 10, 25, 40, 55, 70, 85, 100, 115, 125, 130, 145, 160, 170, 190, 205, 235, 265, and 295 min after the start of drug infusion. CO was measured from the arterial pressure curve (obtained from the arterial line) by using the FloTrac sensor and Vigileo monitor (Edwards Life Sciences, Irvine, CA). CO values were collected at 5-min intervals for further analysis. The algorithm used to calculate CO is based on the principle that pulse pressure is proportional to stroke volume.[12]

PK-PD Analysis

Pharmacokinetic Analysis. Two- and three-compartmental models were fitted to the ketamine concentration data. The best ketamine pharmacokinetic model was extended with one, two, three, or four metabolism compartments and one or two compartments to describe S(+)-norketamine concentration data. The central volume for norketamine is not identifiable; therefore, it was set equal to the central volume of ketamine. The parameters of the central norketamine compartment, rather than the peripheral compartment, could not be reliably estimated, so it was assumed that the amount of S(+)-norketamine in its central compartment is in steady state with respect to the concentrations in the metabolism and peripheral S(+)-norketamine compartments. As a result of this assumption, the S(+)-norketamine formation and elimination rates are not both identifiable (see appendix 2). The S(+)-norketamine formation rate was therefore set equal to the ketamine elimination rate.

Model selection (the number of compartments) was based on a goodness-of-fit criterion (see Statistical Analysis). In the pharmacokinetic analysis, all doses used were per 70 kg. This then defines the pharmacokinetic parameters per 70 kg as well: volumes in l/70 kg and clearances as l/h per 70 kg. These units were chosen to conform those of Herd *et al.*[13]

Pharmacodynamic Analysis. The heat pain vas data were modeled as:

$$VAS(t) = \frac{Baseline}{1 + \left(\frac{C_{ket}(t)}{C_{50,ket}}\right)^{\gamma}} + TRD \cdot t/300 \qquad (1)$$

where Baseline is baseline the predrug VAS value, $C_{ket}(t)$ is the S(+)-ketamine plasma concentration at time t, and $C_{50,ket}(t)$ is the concentration S(+)-ketamine causing 50% effect, and γ is a shape parameter. TRD is a trend coefficient to allow for changes in effect parameters unrelated to S(+)-ketamine; 300 is the duration of the measurement.

The response to the electrical stimulation was modeled by assuming that ketamine inhibits pain perception. Consequently, stronger stimuli are needed during ketamine exposure before the subject presses the pain tolerance button. The inhibition (I) is described by[11,14]:

$$I = \frac{1}{1 + \left(\frac{C_{ket}(t)}{AC_{50,ket}}\right)^{\gamma}} \qquad (2)$$

where $AC_{50,ket}$ is the concentration S(+)-ketamine causing 50% inhibition. Because the subject responds when the pain sensation exceeds the response threshold for pain tolerance, we use equation (3) for the current at time t, E(t):

$$E(t) = E_0 \cdot [1 + (C_{ket}(t)/AC_{50,ket})^{\gamma}] + TRD \cdot t/300 \quad (3)$$

where E_0 is the baseline (predrug) current. We somewhat arbitrarily restricted the data analysis to pain tolerance.

The effect of S(+)-ketamine on cardiac output was modeled as:

$$CO(t) = BLN \cdot \left(1 + 0.2\left(\frac{C_{Ket}(t)}{C_{20,ket}}\right)^{\gamma}\right) + TRD \cdot t/300 \quad (4)$$

where $C_{20,ket}$ is the concentration at which cardiac output is 20% higher than baseline. This value was chosen because it indicates a significant effect and lies midst the measured data range.

To estimate the contribution of S(+)-norketamine to the measured effect, S(+)-norketamine was modeled in additive fashion for all three endpoints. For example, for heat pain intensity:

$$VAS(t) = \frac{BLN}{1 + \left(\frac{C_{ket}(t)}{C_{50,ket}} + \frac{C_{nkt}(t)}{C_{50,nkt}}\right)^{\gamma}} + TRD \cdot t/300 \quad (5)$$

where $C_{nkt}(t)$ is the S(+)-norketamine plasma concentration at time t and $C_{50,nkt}(t)$ is the concentration S(+)-norketamine causing 50% effect.

Statistical Analysis

Data analysis was performed with the statistical package NONMEM VI version 1.2 using ADVAN6 (ICON Development Solutions, Ellicott City, MD).[15] The PK-PD analysis was performed in two stages. From the first stage (pharmacokinetic analysis), empirical Bayesian estimates of the pharmacokinetic parameters were obtained. In the second stage (pharmacodynamic analysis), the pharmacokinetic parameters were fixed to those obtained from the first stage. Model parameters were

Table 1. Characteristics of the Study Population

	All Volunteers	Men	Women
n	20	10	10
Age, yr	21.7 ± 0.5	21.7 ± 1.0	21.7 ± 0.5
Weight, kg	69.4 ± 2.4	75.2 ± 2.4	63.6 ± 3.2
Height, cm	177.2 ± 2.4	184.7 ± 1.7	169.7 ± 2.9
BMI, kg/m^2	22.1 ± 0.5	22.0 ± 0.6	22.1 ± 0.9

Values are mean ± SEM.

BMI = body mass index.

assumed to be lognormally distributed across the population, except TRD, which was normally distributed. Residual error was assumed to have a constant relative error for concentrations and additive error for all effect parameters.

The number of compartments in the pharmacokinetic models was determined by the magnitude of the decrease in minimum objective function value (MOFV) (chi-square-test; $P < 0.01$ was considered significant). In the current analysis, sex and weight were considered as covariates. For pharmacokinetic and pharmacodynamic parameters, a separate male and female parameter was introduced and compared to a combined parameter using the objective function value. Sex dichotomy was accepted when the objective function value improved at the $P < 0.01$ level. For weight, a comparison was made between weight-scaled parameters and nonscaled parameters.

Visual predictive checks were performed to assess the adequacy of the description of both fixed and random effects, by simulating data using the final models and calculating their 5th, 10th, 50th, 90th, and 95th percentiles at all sampling times and comparing them with the corresponding percentiles of the measured data.[16] Variability caused by covariate sex was taken into account by simulating individuals according to the same female/male ratio as in the experimental data.

Results

The anthropometric data of the subjects are given in table 1. All subjects completed the protocol without unexpected or major side effects. After S(+)-ketamine nausea occurred in 80% of subjects (16 of 20), dizziness in 100% of subjects (20 of 20), and hypertension in 100% of subjects (mean blood pressure 150/110 mmHg at the end of ketamine infusion).

Pharmacokinetic Data Analysis

The mean plasma concentrations of S(+)-ketamine and S(+)-norketamine are given in figure 1B. For seven subjects at t = 15 min, the norketamine plasma concentrations were below the lower limit of quantitation (10 ng/ml) but above the detection limit (3 ng/ml); these data were not discarded. A near-linear increase of both agents during the ketamine infusion was followed by an exponential decline upon the termination of the infusion. S(+)-norketamine levels were higher than S(+)-ketamine concentrations within 10 min after the end of the infusion. A clear sex difference was present in the pharmacokinetic data, with higher concentrations for both S(+)-ketamine and S(+)-norketamine in the male compared to the female study population (fig. 1, C and D). The final model used to analyze the pharmacokinetic data are given in figure 2, showing three ketamine compartments (V1-3,ket), three metabolism or transit compartments (M1-3), and two norketamine compartments (V1-2,nkt). Inclusion of three metabolism compartments rather than one improved the MOFV by 8 points; inclusion of a peripheral norketamine compartment improved the MOFV by 539 points (see appendix 3). Inclusion of the covariate sex on CL_1 for S(+)-ketamine and S(+)-norketamine did improve the data fits significantly (ΔMOFV = 17 points). The pharmacokinetic parameter values are given in table 2. The S(+)-ketamine pharmacokinetic values were similar to values observed when the pharmacokinetic model was restricted to just S(+)-ketamine, indicating that combining the analysis with S(+)-norketamine did not affect the S(+)-ketamine analysis (table 2). Weight-scaled parameterization yielded a significant improvement over non–weight-scaled parameterization (ΔMOFV = 21 points). Best, median, and

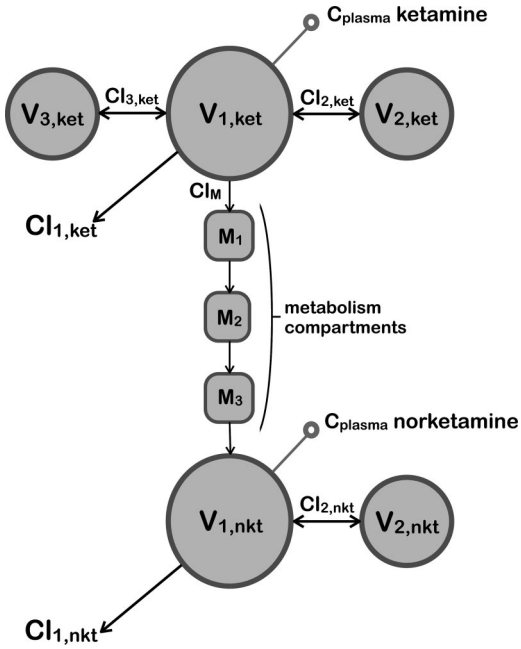

Fig. 2. Schematic representation of the pharmacokinetic model used to analyze the S(+)-ketamine and S(+)-norketamine data. $V_{1,ket}$, $V_{2,ket}$, and $V_{3,ket}$ represent the three compartments for S(+)-ketamine; $V_{1,nkt}$ and $V_{2,nkt}$ represent the two compartments for norketamine. M_1, M_2, and M_3 are the three sequential ketamine metabolism compartments with total mean transit time = $3/K_M$, where K_M = a rate constant (see appendix 2). $Cl_{1–3,ket}$ and $Cl_{1–2,nkt}$ represent the clearances from compartments $V_{1–3,ket}$ and $V_{1–2,nkt}$, respectively. Cl_M is the S(+)-ketamine clearance responsible for the S(+)-norketamine formation. Modifiers: ket = S(+)-ketamine; nkt = S(+)-norketamine.

Table 2. Population Pharmacokinetic Model Parameters

	Combined S(+)-ketamine – S(+)-norketamine Pharmacokinetic Model				S(+)-ketamine Pharmacokinetic Model			
	Θ	SE	ω^2	SE	Θ	SE	ω^2	SE
S(+)-ketamine								
V_1, l*	15.4	2.34	0.320	0.114	15.6	2.62	0.333	0.113
V_2, l*	26.6	2.70	0.117	0.0344	25.1	2.69	0.0871	0.0279
V_3, l*	121	7.57	0.0830	0.0223	119	6.93	0.0788	0.0175
CL_1 male, l/h†	75.1	4.63	0.00683	0.00282	81.4	2.38	0.00745	0.00312
CL_1 female, l/h†	97.3	2.80			98.0	2.80		
CL_2, l/h†	80.6	2.42	‡		143	24.6	‡	
CL_3, l/h†	146.0	15.3	0.0260	0.0126	77.0	5.01	0.0302	0.0150
σ^2	0.00686	0.00129	‡		0.00681	0.00127	‡	
S(+)-norketamine								
MTT, h	0.193	0.00178	0.0661	0.0321				
V_2, l*	163	11.4	0.0743	0.0258				
CL_1 male, l/h†	53.4	4.84	0.0640	0.0187				
CL_1 female, l/h†	79.4	5.94						
CL_2, l/h†	262	23.2	0.0977	0.0444				
σ^2	0.00648	0.00142	‡					

* V units are l per 70 kg; † CL are l/h per 70 kg; ‡ parameter fixed to zero.

Cl_x = clearance of parameter 1, 2, or 3; MTT = mean transit time; σ^2 = within-subject variability (in the log-domain); SE = standard error; Θ = typical parameter value; V_x = volume of compartment 1, 2, or 3; ω^2 = between-subject variability (in the log-domain).

worst pharmacokinetic data fits (determined by R^2, the coefficient of determination) are given in figure 3.

Pharmacodynamic Data Analysis

We observed that in response to the S(+)-ketamine infusion S(+)-ketamine produced analgesia in both heat and electrical pain tests, severe drug high, and an increase in cardiac output (fig. 4). All effect parameters showed a rapid onset during ketamine infusion and a rapid offset upon the termination of the infusion. Ketamine's effect on heat pain unpleasantness was larger than its effect on pain intensity. Both indices showed an increase above baseline after the termination of ketamine infusion (fig. 4A).

Analysis of heat pain unpleasantness and drug high using equations 1 and 5 yielded consistent misfits with the estimated values lagging the measured data. This indicates that the models used in these pharmacodynamic analyses do not give an adequate representation of the ketamine (and norketamine) – effect (heat pain unpleasantness and drug high) relationship. We therefore discarded the data analysis of these parameters and focused on the other endpoints of the study. For S(+)-ketamine *versus* effect (equations 1–4), the pharmacodynamic model parameters of endpoints heat pain intensity, electrical pain tolerance, and CO are presented in table 3. Corresponding best, median, and worst fits are given in figure 5. The PK-PD models adequately described the ketamine-effect data (see also the visual predictive checks in fig. 6). As expected from the observation of an increase in VAS after ketamine infusion, for heat pain intensity (but not electrical pain or

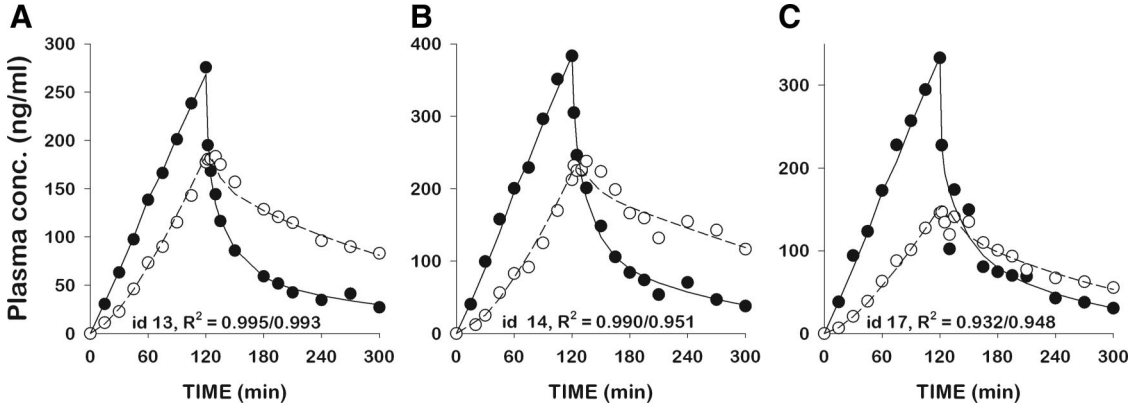

Fig. 3. Pharmacokinetic data fits. Best (*A*), median (*B*), and worst (*C*) data fits of the ketamine and norketamine pharmacokinetic data using the model depicted in Fig. 2. The *closed circles* and *open circles* are the measured S(+)-ketamine and S(+)-norketamine concentrations, respectively; the *lines* through the data are the model fits. Goodness of fit given by R^2 for ketamine/norketamine.

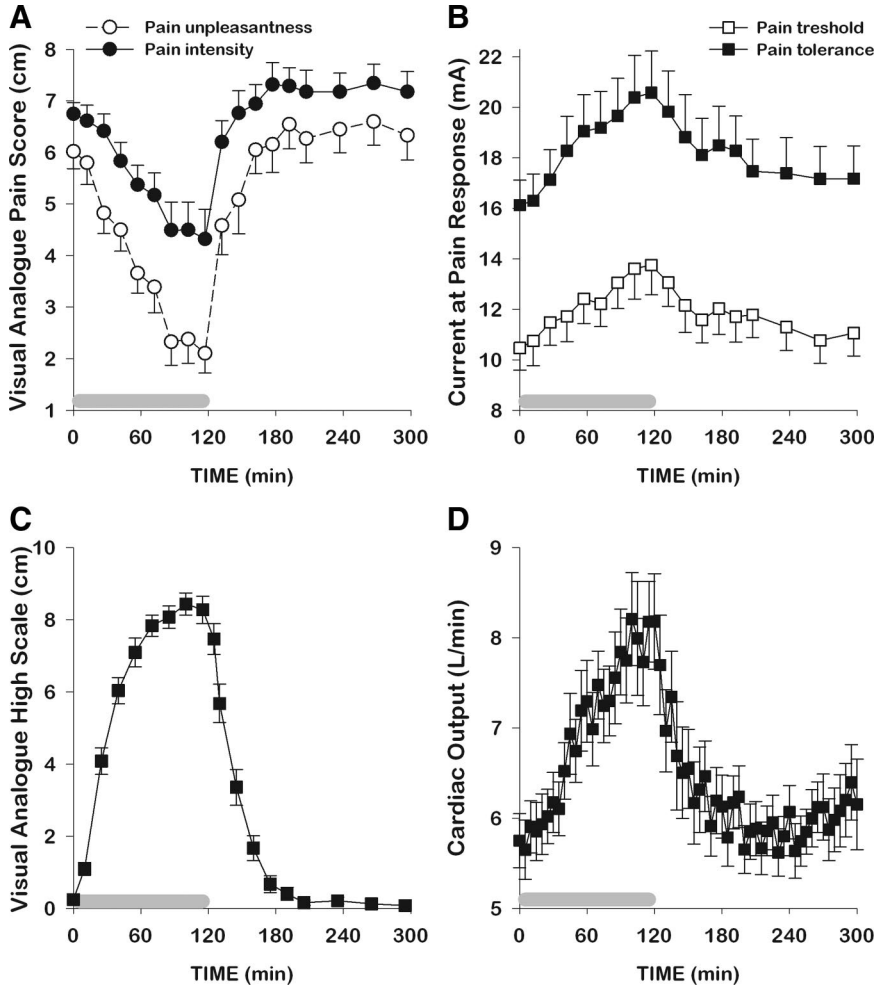

Fig. 4. The pharmacodynamic endpoints of the study. (*A*) Heat pain intensity and unpleasantness scored using a 10-cm visual analogue scale (VAS) ranging from 0 (no pain) to 10 (most intense pain or most unpleasant pain experience). (*B*) Electrical pain threshold and tolerance. (*C*) Drug high scores using a 10-cm VAS. (*D*) Cardiac output. Values are mean ± SEM. The *gray bars* denote the time of S(+)-ketamine infusion (0–120 min).

cardiac output) there was a significant positive trend term present. The trend term corresponds to a significant increase in VAS of 0.9 cm from baseline until the end of the study. Note however that the SE and interindividual variability for TRD were high. For electrical pain and CO, the trend parameters were not significantly different from zero and consequently fixed to zero. For none of the pharmacodynamic model parameters, there was a significant sex effect.

S(+)-ketamine produced a 20% increase in CO at 134 ng/ml; 50% effect on pain parameters occurred at 373 ng/ml for heat pain (*i.e.*, the concentration causing 50% inhibition in pain perception) and 2.2 μg/ml for electrical pain (*i.e.*, the concentration causing 50% inhibition of pain signal propagation), indicating that S(+)-ketamine is six times more potent in the heat pain assay.

There was no consistency in the contribution of S(+)-norketamine to measured effect (as analyzed by equation 5). A significant contribution could be demonstrated in just a minority of subjects and was not consistent among endpoints or magnitude. The overall picture that emerges from the analysis was that S(+)-norketamine contributes little to the overall effect and that the measurements are all well described by just taking S(+)-ketamine into account.

Discussion

The main findings of our study in human volunteers are (1) S(+)-ketamine displays sex differences in its pharmacokinetics with higher plasma concentrations of S(+)-ketamine and S(+)-norketamine in men compared to women; (2) upon the termination of S(+)-ketamine infusion, the plasma concentrations dropped rapidly, causing the plasma concentrations of S(+)-norketamine, ketamine's major metabolite, to exceed those of S(+)-ketamine; (3) ketamine produced analgesia in heat and electrical pain tests albeit with six times greater potency in the heat pain test; (4) in the heat pain test but not the electrical pain test, analgesia was followed by hyperalgesia after the 2-h IV infusion period; (5) over the dose range tested (0–320 ng/ml), ketamine produced a 40–50% increase in cardiac output; (6) a significant consistent contribution of S(+)-norketamine to overall effect was not detected.

Table 3. Population Pharmacodynamic Model Parameters

	Θ	SE	ω^2	SE
Heat pain intensity				
BLN, cm	6.67	0.253	0.0221	0.00703
C_{50}, ng/ml	373	64.0	0.398	0.191
γ	2.53	0.343	0.163	0.132
TRD, cm	0.882	0.380	2.14	1.28
σ^2	0.490	0.0551		
Electrical pain tolerance				
BLN, mA	15.5	0.007	0.7019	0.0250
AC_{50}, μg/ml	2.20	0.034	0.916	0.549
γ	0.693	0.0109	*	
TRD, mA	*	—	4.88	4.83
σ^2	6.36	4.08		
Cardiac output				
BLN, l/min	5.32	0.257	0.0288	0.00707
C_{20}, ng/ml	134	0.143	1.40	0.388
γ	1 (FIX)	*	0.119	0.0574
Covariance between C_{20} and γ			0.397	0.133
TRD, L/min	*	—	1.15	0.526
σ^2	0.651	0.165		

* Parameter fixed to zero.

AC_{50} = the ketamine concentration causing a 50% inhibition of electrical pain perception; BLN = baseline value; C_{20} = ketamine concentration causing 20% effect; C_{50} = ketamine concentration causing 50% effect; γ = a shape factor; σ^2 = within-subject variability (in the log-domain); SE = standard error; Θ = typical parameter value; TRD = trend coefficient; ω^2 = between-subject variability (in the log-domain).

Pharmacokinetics

The pharmacokinetic parameters for S(+)-ketamine derived from our pharmacokinetic models (table 2) were in general agreement with values presented in the literature on S(+)-ketamine in adult surgical patients and healthy volunteers.[17–20] We are the first to study and observe sex differences in the kinetic profile of S(+)-ketamine and its major metabolite. The observed higher plasma concentrations in men are the result of a difference in elimination clearance with 20% higher clearances in women (table 2). The cause for the difference in clearance between the sexes remains unknown, but it may be related to sex differences in drug plasma protein binding, liver perfusion, and/or activity of the 3A4 isoform of cytochrome P450 (the major metabolic pathway *via* which ketamine is metabolized into norketamine).[21] However, differences in CYP3A4 activity seem unlikely because a sex-effect on metabolism would have resulted in the combination of low S(+)-ketamine and high S(+)-norketamine concentrations (*i.e.*, a high metabolizer sex) or *vice versa* (*i.e.*, a low metabolizer sex).

Herd *et al.*[13] modeled the metabolism of racemic ketamine into norketamine in a pediatric patient population. They estimated a mean transit time (the time spent in intermediate or metabolism compartments between the central ketamine and norketamine compartments) of about 0.11 h, which is lower than we estimated (0.19 h). However, their pharmacokinetic model differed from ours with just one peripheral ketamine compartment and no peripheral norketamine compartment. In contrast to Herd *et al.*, we added a peripheral norketamine compartment and observed a significant improvement in MOFV (539 points). We were unable to estimate the amount of ketamine that was converted into norketamine, which is most likely related to the pharmacokinetic (distribution *vs.* elimination) properties of norketamine. The present norketamine pharmacokinetic parameter estimates are conditional on the assumptions made. Accurate and complete characterization of norketamine pharmacokinetics is only possible when data derived from the separate administration of the metabolite are available. For example, we previously were able to estimate that 5–10% of morphine is metabolized into morphine-6-glucuronide as distinct pharmacokinetic data sets of both agents were available to us.[14,22] As far as we know, there is currently no norketamine (S(+)-norketamine or racemic mixture) for human use available.

Pain Test—Hyperalgesia

While pain intensity is associated with pain sensory processing, pain unpleasantness is linked to affective pain processing.[23,24] These distinct pain dimensions are associated with activation of separate regions in the brain with different drug sensitivities.[23] For example, Oertel *et al.*[23] showed that brain regions that process the affective dimensions of pain to be most sensitive to opioids (*i.e.*, their activation disappears at lower opioid concentrations than in regions involved in processing the sensory intensity of pain). Similarly, low-dose S(+)-ketamine has a predominant effect on the midcingulate cortex, which processes the affective components of pain.[24] This suggests that the pronounced ketamine high (euphoria) interacts strongly with the emotional coloring of pain (dampening pain unpleasantness) rather than interacting with sensory processing. In agreement with the above, we observed that ketamine had a greater effect on pain unpleasantness than on pain intensity (fig. 4A). In contrast to electrical pain, a small hyperalgesic effect was present in the heat pain intensity data that was modeled by a trend term (TRD in equation 1). As there was a small predication bias for VAS values after 120 min in the visual predictive check (at least for the 50th percentile) for the heat pain data we may have underestimated the hyperalgesic component somewhat in our model. Adding a separate component with hyperalgesic properties when ketamine infusion is terminated would reduce or remove the observed bias. Attempts to do so by us were successful, but we refrained from presenting these models as they lack a firm pharmacological/physiologic basis at present. The observation of hyperalgesia after a short ketamine infusion was unexpected. Ketamine is commonly associated with antihyperalgesia,[25–27] and is used frequently in combination

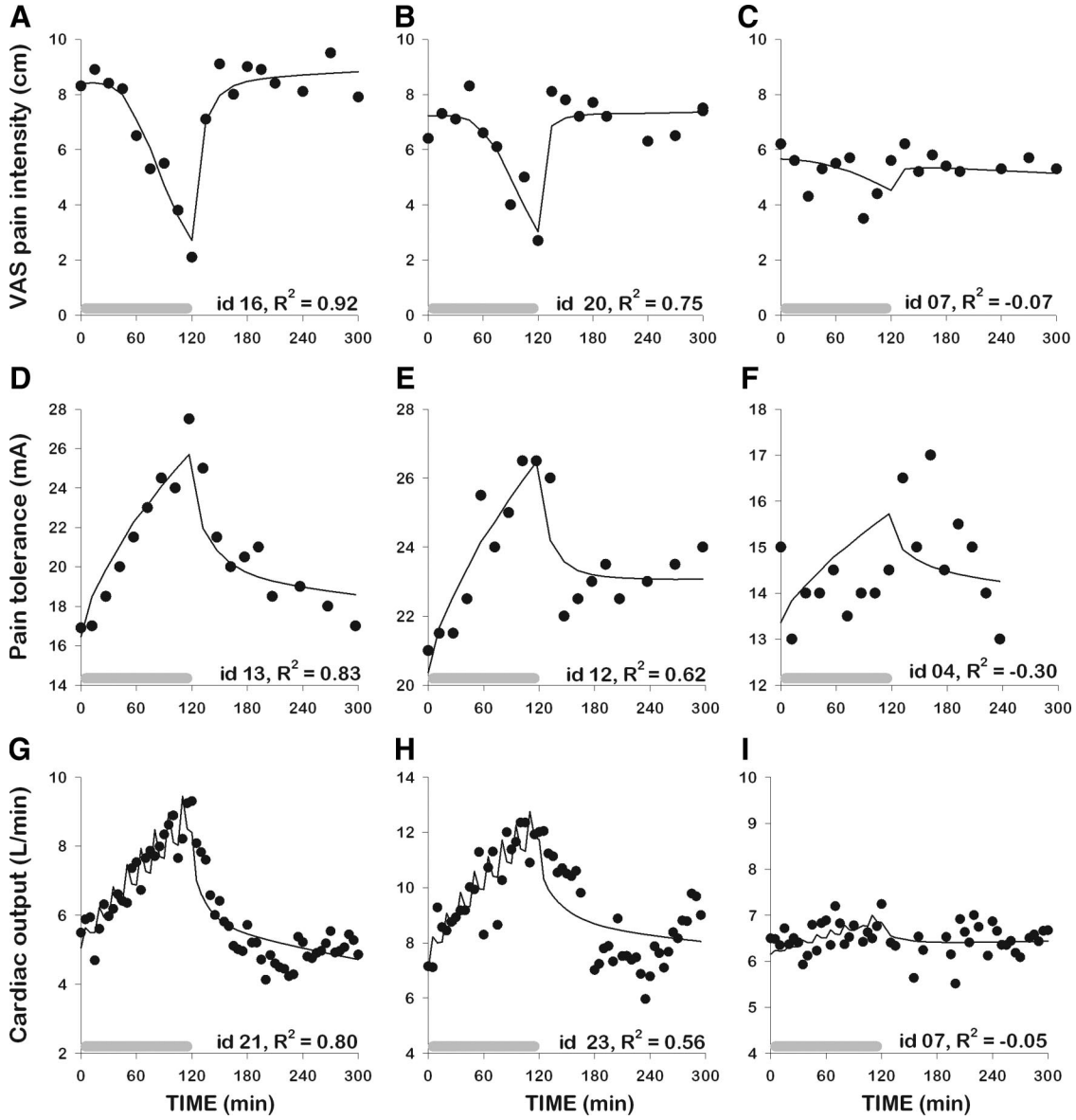

Fig. 5. Pain intensity, pain tolerance, and cardiac output data fits. *A–C*: Best (*A*), median (*B*), and worst (*C*) data fits of ketamine-pain intensity data. The *dots* represent the measured pain intensity (using a visual analogue scale [VAS] from 0 to 10). *D–F*: Best (*D*), median (*E*), and worst (*F*) data fits of the ketamine-pain tolerance data. The *dots* represent the measured pain tolerance (in mA). *G–I*: Best (*A*), median (*B*), and worst (*C*) data fits of the ketamine-cardiac output data. The *dots* are the cardiac output measurements. *The continuous lines* are the data fits; the *gray bar* represents the S(+)-ketamine infusion period. Goodness of fit given by R^2.

with opioid analgesics to prevent opioid-induced hyperalgesia and/or the development of chronic pain in postoperative patients.[2–5] Ketamine does so by blocking NMDA receptors, preventing peripheral and central sensitization. However, there are reports that the noncompetitive NMDA receptor antagonist (+)-MK801 can cause antianalgesic effect in rodents.[28,29] It is postulated that during exposure to NMDA blocking agents excitatory amino acids accumulate in the cerebrospinal fluid and activate non-NMDA excitatory receptors.[28] Other possible causes for the observed antianalgesia in our data are activation of opioid receptors (analogous to opioid-induced hyperalgesia),[30] and/or a rebound increase in activation of the NMDA receptor in response to a rapid decrease in antagonist concentration at the receptor site.[28] We do believe that for now the hyperalgesia data should be interpreted with some caution, given the large variability in TRD parameter among subjects. Additional studies are needed to explore this matter to further extent. It is of interest to note that Mitchell describes a cancer pain patient that developed severe hyperalgesia and allodynia after termination of a ketamine infusion similar to what we observed in our subjects for heat pain intensity.[31]

Sex Differences

We observed sex differences in cardiac output and heat pain related indices with a greater ketamine effect

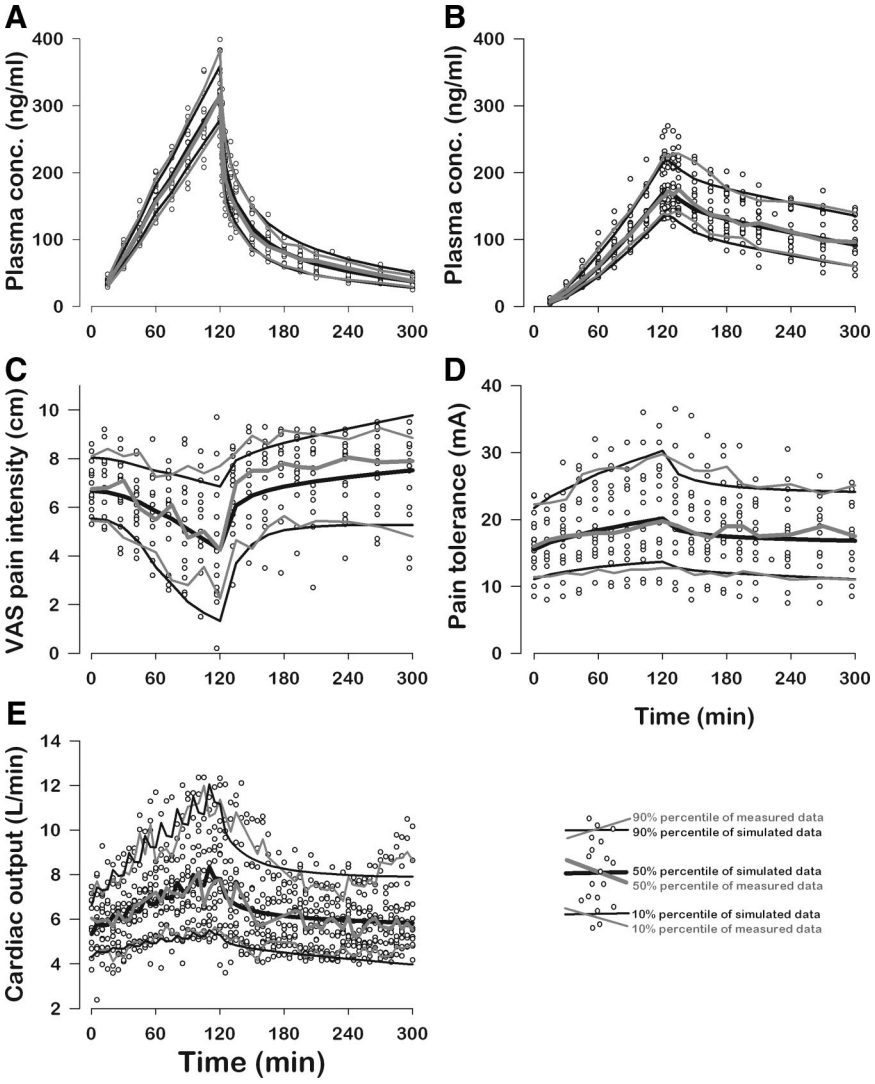

Fig. 6. Predictability and accuracy of the pharmacokinetic/pharmacodynamic model outcomes. Simulations performed with the S(+)-ketamine input as used in the study in healthy volunteers. (*A*) S(+)-ketamine concentration; (*B*) S(+)-norketamine concentration; (*C*) heat pain intensity; (*D*) electrical pain tolerance; (*E*) cardiac output. The *lines* represent the 10th, 50th, and 90th percentiles for simulated responses (*black lines*) and measured responses (*gray lines*). The *symbols* are the actual observations in the healthy volunteers. VAS = visual analogue scale.

in men compared to women. An example of the effect of sex on cardiac output is given in figure 7. Our PK-PD models indicated that all observed sex differences in effect were the result of greater plasma S(+)-ketamine (and S(+)-norketamine) concentrations in men and not to differences in pharmacodynamic model parameters. These observations exemplify the need for plasma drug concentrations (or even better brain concentrations) when studying sex differences in drug effect. In humans, there is just one study in the literature exploring the existence of sex differences in ketamine effects. Examining behavioral data from 11 placebo-controlled studies, Morgan *et al.*[32] detected that men show a greater performance decrement in cognitive functions (such as verbal learning tasks) after ketamine administration than women. Plasma drug concentrations were not obtained, so we remain uninformed about whether these results are related to differences in pharmacokinetics or pharmacodynamics; our results suggest that the sex-related differences in performance change from ketamine were driven by pharmacokinetics.

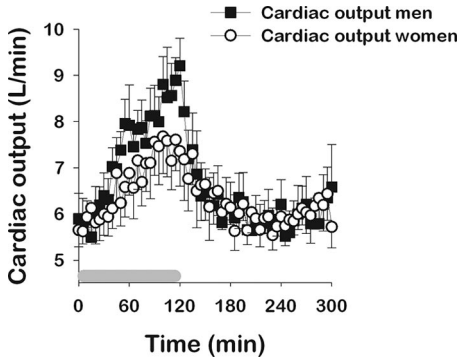

Fig. 7. Effect of S(+)-ketamine on cardiac output in men *versus* women. Data are mean ± SEM. The *gray bars* denote the time of S(+)-ketamine infusion (0–120 min).

Norketamine Contribution

Norketamine, ketamine's major metabolite, is a noncompetitive antagonist of the NMDA receptor and contributes to ketamine analgesia.[13,33–35] Studies that examined norketamine's contribution to ketamine analgesia

do not provide quantitative information.[13,33,34] We were unable to estimate a significant contribution of S(+)-norketamine to the overall effects we measured by using an additive pharmacodynamic model (equation 5). Given the relatively low potency of S(+)-norketamine on acute pain in animal studies (S(+)-norketamine has a potency of just 20–30% of S(+)-ketamine on the tail withdrawal test in rats [unpublished observation from Aurora Morariu, M.D., Ph.D., Maarten Swartjes, B.Sc., and Albert Dahan, M.D., Ph.D., Leiden, The Netherlands, March 2009]), the S(+)-norketamine concentrations produced during just 2 h of low-dose S(+)-ketamine infusion were probably too low to cause a significant analgesic effect. Furthermore, to get an accurate estimation of norketamine's contribution to ketamine's effect an indication of its potency in humans is a prerequisite. Further studies using manipulation of ketamine hepatic metabolism are currently being performed in our laboratory to further explore the issue of norketamine analgesic effect in humans.

Onset/Offset Times—Comparison with the Literature

Our study was not designed to estimate ketamine's blood-effect-site equilibration half-life (t½ k_{e0}). The effects of S(+)-ketamine seemed to follow its plasma concentrations instantaneously (or sometimes even preceded the change in concentration), suggesting a small value for t½ k_{e0} (*cf.* Herd *et al.*[36]: no hysteresis is observed between venous ketamine concentration and electroencephalogram slowing). It is of interest to review C_{50} values derived from ketamine PK-PD modeling in humans reported in the literature. In adults, Schüttler *et al.*[36] estimated an EC_{50} of 800 ng/ml or greater for adequate anesthesia with S(+)-ketamine using slowing of the electroencephalogram (changes in median frequency) as endpoint. This suggests that at least two times greater S(+)-ketamine concentrations are required to induce anesthesia compared to heat pain analgesia, whereas the EC_{50} is in the same range as we estimated for electrical pain tolerance. Herd *et al.*[36] performed a PK-PD study in children (aged more than 6 yr) on racemic ketamine for procedures in the emergency department. C_{50} values of 500 and 440 ng/ml were estimated for arousal and recall memory, respectively. A direct comparison with our data is difficult because of the age effect, different endpoints, and use of racemic ketamine. An interesting observation in the latter study is that t½ k_{e0} was estimated to be 11 s (95% confidence interval 7–20 s), which is in close agreement with our findings and those of Schüttler *et al.*[36]

Side Effects—Cardiac Output

Ketamine is notorious for its psychomimetic and cardiovascular side effects such as hallucinations, severe drug high, tachycardia, and hypertension.[1,37,38] At low-dose S(+)-ketamine, we observed nausea, dizziness, drug high, hypertension, and an increase in cardiac output. To the best of our knowledge, we are the first to quantify the effect of S(+)-ketamine on CO showing an increase from 5.5 to 8.2 l/min over the dose studied (0–320 ng/ml) with a C_{20} (a 20% increase in CO) of 134 ng/ml. We did not study racemic ketamine as comparator in our study, and we are therefore not able to draw any conclusions on possible differences in potency between S(+)-ketamine and racemic ketamine on the various side effects. Side effects such as mentioned above restrict the use of ketamine. They are linked to ketamine's effect at the NMDA receptor[1,39]; it is therefore doubtful whether a potent NMDA receptor antagonist will be developed that is without these particular phenylcyclidine-like effects.

Concluding Remarks

Finally, our study did not include a placebo arm; our intentions were to compare ketamine effect on sex and among different pharmacodynamic endpoints. To get an indication of the effect of placebo, we performed an additional set of experiments in ten subjects (five men and five women) on heat and electrical pain testing (data not shown). No significant effect was seen in the heat pain test, whereas a small and slowly evolving analgesic effect was in the electrical pain test (maximum effect about 20% above baseline). These findings are in close agreement with earlier observations from our laboratory (see fig. 1 of Olofson *et al.*[11]). These data then indicate that our observations of analgesia and hyperalgesia are related to the study compound and not to other factors. When comparing the ketamine responses with those obtained from placebo, our conclusions would not change.

Appendix 1: Analyses of S-(+)ketamine and its Main Metabolite S-(+)desmethyl-ketamine in Human Plasma by High Performance Liquid Chromatography with Ultraviolet Detection

Calibration

For the construction of S(+)-ketamine and S-(+)-desmethyl-ketamine (= S(+)-norketamine) calibration lines, 25-μl standard solutions (in ethanol) of both agents were added to 0.5 ml of blanc heparin plasma to yield concentration ranges of 13.9–556 ng/ml and 6.95–278 ng/ml for ketamine and desmethyl-ketamine, respectively. The S(+)-ketamine and S(+)-norketamine solid substances were obtained from Park-Davis (Dallas, TX) and Tocris (St. Louis, MO), respectively.

Extraction Procedure

To all samples, 25 μl of ethanol was added to compensate for the ethanol in the standard solution. Subsequently, 25 μl of internal standard solution (nortilidine [Park Davis] in ethanol) was added, after

which the samples were mixed on a vortex shaker. Next, 100 μl of 0.1-N NaOH and a 5-ml mixture of pentane-isopropanol (95:5) were added. The extraction of all desired compounds was performed on a Vibrax multimixer (Dijkstra Vereenigde, Lelystad, The Netherlands). After centrifugation (4,000 rounds/min for 15 min; Heraeus Christ Minifuge GL, Boom, Meppel, The Netherlands), the organic upper layer was transferred into another tube, and the components were back-extracted into 0.6 ml of 0.4-N HCl by vortexing for 3 min. After another centrifugation, the organic layer was aspirated, and the HCl layer was transferred into another tube and dried in a dry block and sample concentrator (Wilten Instrumenten, Etten-Leur, The Netherlands) at 50°C under a gentle stream of nitrogen.

Analysis

The residue was resolved in mobile phase and transfered into a High Performance Liquid Chromatography vial, and 25 μl was injected using a Midas autoinjector (Spark Holland, Emmen, The Netherlands) on a Gemini C18 column (3-μm C18 particles, 15-cm length × 3-mm internal diameter; article number OOF-4439-YO; Phenomenex, Utrecht, The Netherlands) at 40°C. The mobile phase was a mixture of phosphate buffer 0.03 N:Acetonitril (88:12) at pH = 3.0. The eluent was monitored at 195 nm with a PDA100 photodiode-array-detector (Dionex, Amsterdam, The Netherlands).

Concentrations

The lower limit of quantitation was 10 ng/ml, and the lower limit of detection was 3 ng/ml for both analytes.

Appendix 2: Differential Equations for Ketamine and Norketamine Pharmacokinetics

The pharmacokinetic parameters (volumes and clearances) were converted to rate constants for NONMEM's $DES block. Part of this block is given:

$DES

$$\mathrm{DADT}(1) = \mathrm{K21}^*\mathrm{A}(2) + \mathrm{K31}^*\mathrm{A}(3) - (\mathrm{K10} + \mathrm{K12} + \mathrm{K13})^*\mathrm{A}(7)$$

$$\mathrm{DADT}(2) = \mathrm{K12}^*\mathrm{A}(2) - \mathrm{K21}^*\mathrm{A}(2)$$

$$\mathrm{DADT}(3) = \mathrm{K13}^*\mathrm{A}(1) - \mathrm{K31}^*\mathrm{A}(3)$$

$$\mathrm{DADT}(4) = \mathrm{K14}^*\mathrm{A}(1) - \mathrm{K45}^*\mathrm{A}(4)$$

$$\mathrm{DADT}(5) = \mathrm{K45}^*\mathrm{A}(4) - \mathrm{K45}^*\mathrm{A}(5)$$

$$\mathrm{DADT}(6) = \mathrm{K45}^*\mathrm{A}(5) - \mathrm{K45}^*\mathrm{A}(6)$$

$$\mathrm{DADT}(7) = \mathrm{K45}^*\mathrm{A}(6) + \mathrm{K45}^*\mathrm{A}(6) - (\mathrm{K70} + \mathrm{K78})^*\mathrm{A}(7)$$

$$\mathrm{A7} = \mathrm{K45}^*\mathrm{A}(6) + \mathrm{K87}^*\mathrm{A}(8)/(\mathrm{K70} + \mathrm{K78})$$

$$\mathrm{DADT}(8) = \mathrm{K78}^*\mathrm{A7} - \mathrm{K87}^*\mathrm{A}(8)$$

Parameter estimation (given the present data) of the model in NONMEM is possible by using the steady-state solution for A7, which was obtained by solving the equation DADT(7) = 0. Note that compartment 7 is not used and could be removed. We present it here to illustrate the similarity between a steady-state solution and one with a differential equation. The transfer function describing the relationship among A(6), A(8), and A(7) may now be written as:

$$\mathrm{A7}(s) = \mathrm{K45} \cdot \mathrm{A} \cdot (6)(s + \mathrm{K87})/(s \cdot (\mathrm{K70} + \mathrm{K78}) + \mathrm{K70} \cdot \mathrm{K87})$$

in which K45, K70, K78, and K87 are not simultaneously identifiable; only three parameters can be estimated (but note that there would be two estimable parameters without the peripheral norketamine compartment). We therefore fixed K14 = K10. This solution applies in the case that K78 is large with respect to changes in A(6) and A(8) so that a lag in central norketamine amount A(7) with respect to the metabolism compartment amount A(6) and peripheral norketamine compartment amount A(8) cannot be identified. K45 equals the rate constant K_M of the metabolism compartments; the mean tranit time (MMT) in the metabolism compartments equals $3/K_M$.

Appendix 3: Simulation Study—One or Two Norketamine Pharmacokinetic Compartments?

Herd *et al.*[13] modeled the ketamine and norketamine pharmacokinetic data by using a pharmacokinetic model that, with respect to the norketamine compartments, differs from our model in that it has only one norketamine compartment. We used an additional peripheral norketamine compartment (fig. 2) and observed a large improvement in minimal objective function when comparing the two models. To further assess the validity of our model assumptions, we performed a simulation study in which we generated a pharmacokinetic data set by using our final model. This data set was then analyzed by using a model lacking the norketamine peripheral compartment and our final model

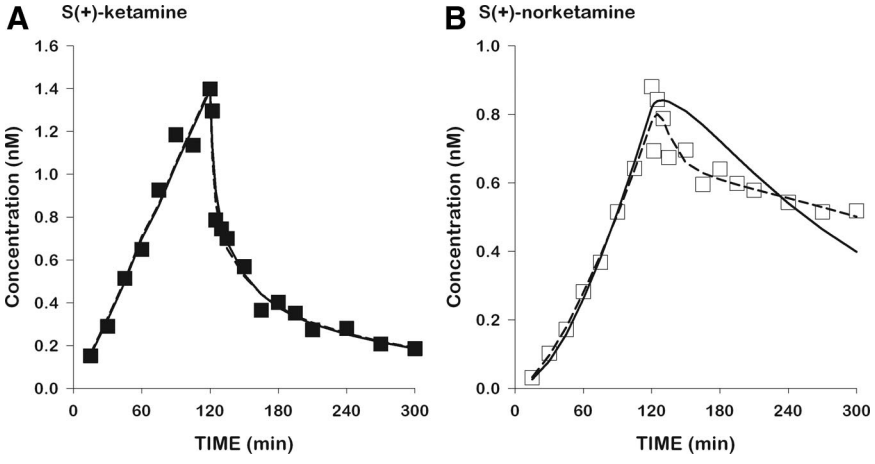

Fig. 8. Simulation pharmacokinetic analysis using one or two norketamine compartments. Using a simulated data set, the ketamine (*A*) and norketamine (*B*) concentrations were analyzed by using three ketamine compartments and one (*continuous lines*) or two (*dashed lines*) norketamine compartments. There is a dramatic improvement in norketamine data fit when a two-compartment norketamine model is applied.

(with a central and a peripheral norketamine compartment). The results are given in figure 8, showing that the fit without a peripheral compartment is inadequate. In contrast, adding the peripheral norketamine compartment, with the assumption of immediate equilibration of the central compartment, is adequate (fig. 8B). This simulation exemplifies that the difference in descriptive characteristics of the one and two norketamine compartments is highly significant. The conversion fraction of ketamine into norketamine was a parameter in the pharmacokinetic model. With our data, and the fast central compartment equilibration, the conversion fraction is not estimable.

Differences between our data and those of Herd *et al.* [13] may explain the differences in model outcome. Differences exist in the age of the subjects tested in our study (older than 18 yr) and those of Herd *et al.* (mean age 8.3 yr, range 1.5–14 yr), the use of the S(+)-enantiomer in our study and racemic ketamine in the study of Herd *et al.*, the duration of ketamine infusion, the sampling scheme, and the fact that we obtained arterial blood samples and Herd *et al.* obtained venous samples. We applied a short-term ketamine infusion and performed frequent arterial sampling; therefore, we needed an additional peripheral norketamine compartment to adequately describe the pharmacokinetic data. In contrast, the study of Herd *et al.* is more extended in duration, with less frequent venous sampling. Consequently, they were not required to separate a central/peripheral norketamine component to adequately describe their data. Further studies are needed to clarify this matter.

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