Population pharmacokinetic–pharmacodynamic modeling of ketamine-induced pain relief of chronic pain

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Abstract

Aims: Pharmacological treatment of chronic (neuropathic) pain is often disappointing. In order to enhance our insight in the complex interaction between analgesic drug and chronic pain relief, we performed a pharmacokinetic–pharmacodynamic (PK–PD) modeling study on the effect of S(+)-ketamine on pain scores in Complex Regional Pain Syndrome type 1 (CRPS-1) patients.

Methods: Sixty CRPS-1 patients were randomly allocated to receive a 100-h infusion of S(+)-ketamine or placebo. The drug infusion rate was slowly increased from 5 mg/h (per 70 kg) to 20 mg/h based upon the effect/side effect profile. Pain scores and drug blood samples were obtained during the treatment phase and pain scores were further obtained weekly for another 11 weeks. A population PK–PD model was developed to analyze the S(+)-ketamine-pain data.

Results: Plasma concentrations of S(+)-ketamine and its metabolite decreased rapidly upon the termination of S(+)-ketamine infusion. The chance for an analgesic effect from ketamine and placebo treatment was 67 ± 10% and 23 ± 9% (population value ± SE), respectively. The pain data were well described by the PK–PD model with parameters $C_{50} = 10.5 ± 4.8$ ng/ml (95% CI 4.37–21.2 ng/ml) and $t_1/2$ for onset/set = 10.9 ± 4.0 days (5.3–20.5 days).

Discussion: Long-term S(+)-ketamine treatment is effective in causing pain relief in CRPS-1 patients with analgesia outlasting the treatment period by 50 days. These data suggest that ketamine initiated a cascade of events, including desensitization of excitatory receptor systems in the central nervous system, which persisted but slowly abated when ketamine molecules were no longer present.

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1. Introduction

Chronic pain yearly affects the quality of life of an increasing number of patients. Various tools are at hand to treat chronic pain patients, but their efficacy and in particular that of pharmacological treatment is often disappointing (Borsook, 2009; Mogil, 2009; Kissin, 2010). This is especially true for neuropathic and inflammatory pain syndromes, including Complex Regional Pain Syndrome type 1 (CRPS-1). CRPS-1 is a chronic pain syndrome which involves severe pain in one or more extremities after local trauma or surgical intervention and is often accompanied by disability, immobility and the loss of quality of life (Veldman et al., 1993). In the Netherlands the incidence of CRPS-1 is 26:100,000 person years, predominantly affecting women (De Mos et al., 2007). While a variety of treatments (pharmacological, physiotherapy, spinal cord stimulation) has been applied to this syndrome, randomized controlled trials indicate limited effectiveness (Borsook, 2009; Sigtermans et al., 2009a). One approach to better understand the interaction between a pharmacological intervention and effect is pharmacokinetic–pharmacodynamic (PK–PD) modeling (Danhof et al., 2008). In a first approach we here apply PK–PD modeling to the pharmacological treatment of CRPS-1 patients. Sixty patients were randomly assigned to receive either a continuous 4-day (100 h) infusion of the N-methyl-D-aspartic acid (NMDA) receptor antagonist S(+)-ketamine or placebo and were followed for 11 weeks following their treatment week (=week 0; total duration of the study = 12 weeks). We previously reported the descriptive analysis of these data, i.e., significant pain relief during treatment with S(+)-ketamine, greater than placebo, which subsequently slowly dissipated over the 11 weeks following treatment (Sigtermans et al., 2009a). Here, we performed three distinct analyses: a population pharmacokinetic analysis; a population pharmacodynamic analysis (which allowed the estimation of the chance for effect versus no effect from treatment from S(+)-ketamine or placebo), and finally a PK–PD analysis.
in ketamine responders (allowing for the estimation of S(+)-ketamine’s potency of chronic pain and estimation of a rate constant for effect onset/offset).

2. Methods

2.1. Patients and treatment

Sixty patients diagnosed with CRPS-1 were randomized to receive intravenous S(+)-ketamine (Ketanest S, Pfizer BV, Capelle aan den IJssel, The Netherlands) or placebo (NaCl 0.9%) after approval of the protocol by the local human ethics committee (Commissie Medische Ethiek, PO Box 9600, 2300 RC Leiden, The Netherlands). The infusion lasted 100 h from Monday morning 8 AM until Friday of the protocol by the local human ethics committee (Commissie Medische Ethiek, PO Box 9600, 2300 RC Leiden, The Netherlands). The infusion could be increased by 0.6 μg kg⁻¹ min⁻¹ pending absence of unacceptable side effects. The maximal infusion rate that was allowed was 7.2 μg kg⁻¹ min⁻¹ (this is 30 mg/h for a 70 kg patient). Three times a day one of the investigators judged whether the infusion rate could be increased (or not) depending on pain relief and side effects (when pain relief was insufficient the infusion could be increased by 0.6 μg kg⁻¹ min⁻¹ pending absence of unacceptable side effects). The maximal infusion rate that was allowed was 7.2 μg kg⁻¹ min⁻¹ (this is 30 mg/h for a 70 kg patient). In case of unacceptable side effects (drug high, hallucinations, nausea/vomiting), the infusion rate could be decreased but was later increased when pain relief was insufficient. In case of full pain relief (i.e., NRS = 0) the infusion rate remained unchanged. During the treatment period pain scores were obtained at three times per day using a Numerical Rating Score (NRS) ranging from 0 (= no pain) to 10 (= unbearable pain). Thereafter pain scores were obtained at 1 week intervals for 11 weeks (total study duration is 12 weeks). Two to four times per day a venous blood sample was obtained for measurement of S(+)-ketamine and S(+)-norketamine concentrations. This was done prior to a change in infusion rate or when no change was applied, at random times. Plasma was separated within 15-min of blood collection and stored at −25 °C until analysis. Analysis was by high performance liquid chromatography as described previously (Sigtermans et al., 2009b). The lower limit of quantitation was 10 ng/ml, the lower limit of detection was 3 ng/ml, for both analytes.

The diagnosis of CRPS-1 was based on the criteria of the International Association for the Study of Pain (Merskey and Bogduk, 1994; Bruehl et al., 1999), that includes: the presence of an initiating noxious event or cause for immobilization; continuing pain, allodynia or hyperalgesia; presence at some time of edema, changes in skin perfusion and/or abnormal sudomotor activity in the region where pain is felt; exclusion of other conditions that could account for the pain and dysfunction. We excluded patients that had a pain score of 5 or less, used strong opioid medication, were aged 17 years or less, were pregnant or lactating, had an increased intracranial pressure or had a serious medical or psychiatric disease. Pain medication that was allowed was paracetamol, non-steroid anti-inflammatory drugs, selective serotonin re-uptake inhibitors, tramadol, amitryptillin, and pregabalin or gabapentin. These drugs were kept constant throughout the 3-month study period. A descriptive analysis of the data has been presented previously (Sigtermans et al., 2009a).

2.2. Pharmacokinetic analysis

A two-compartmental model was used to fit the ketamine concentration data (Herd et al., 2007). The model was extended with one norketamine compartment to simultaneously fit the ketamine and norketamine data. Because the norketamine compartment volume and clearance are not simultaneously identifiable, the norketamine volume was set equal to the ketamine central compartment volume. Furthermore, the fraction (F) of ketamine converted to norketamine was estimated (but note that F depends on the assumption of equal central volume sizes). Covariate weight (WT) was incorporated according to Holford (1996), so volumes were scaled with WT/70, and clearances with (WT/70)⁰.⁷⁵. Concentrations were assumed to have constant relative intra-individual error.

The inter-individual error of the PK model parameters was modeled as log-normally distributed. To assess the accuracy of the PK model, we calculated the median of the percentage performance error (PE) and median of the absolute performance error (APE) (Varvel et al., 1992), where

\[
PE(ij) = \frac{C_{\text{MEAS}}(ij) - C_{\text{PRED}}(ij)}{C_{\text{PRED}}(ij)} 	imes 100\%
\]

\[
APE(ij) = \frac{|C_{\text{MEAS}}(ij) - C_{\text{PRED}}(ij)|}{C_{\text{PRED}}(ij)} 	imes 100\%
\]

and \(ij\) is the \(j\)th measured or population predicted concentration (measured = \(C_{\text{MEAS}}\), predicted = \(C_{\text{PRED}}\)) of the \(i\)th patient.

2.3. Pharmacodynamic analysis

A separate time series analysis was performed (i) to allocate data sets to be used in the PK–PD analysis and (ii) to get informed on the match between treatment and effect, allowing calculation of the chance of effect/no effect when ketamine (i.e., ketamine responder/non-responder) or placebo (i.e., placebo responder/non-responder) were given. A non-response was defined as NRS remains at baseline (R1), or a decreases in NRS in the treatment week but NRS returns to baseline in the following week (R2). A response was defined as a treatment effect in week 0 followed by a slow return to baseline (R3), or a full analgesic effect within 2 weeks to an NRS of 0, which persists in the following weeks (R4).

The four different types of responses (R1–R4) and their probabilities were defined by a mixture model constructed in NONMEM (see Appendix A):

\[
\text{NRS}(T) = \text{BLN} - \text{EFF}(0) \cdot \text{FAC}^T,
\]

so that

\[
\text{EFF}(T + 1) = \text{FAC} \cdot \text{EFF}(T) + \epsilon,
\]

where \(T\) is the week following the treatment (\(T = 0\) is treatment week), \(\text{EFF}(0)\) the treatment effect observed at the end of week 0, \(\text{BLN}\) is baseline (i.e., pre-treatment) NRS, and FAC an exponential autoregressive factor indicating the fraction of NRS at \(T + 1\) relative to \(T\). Assume baseline NRS = 8, EFF at week 0 = 6 and FAC = 0.8, then at the end of the treatment week: \(\text{NRS}(0) = 8 - 6 = 2\); at the end of week 1: \(\text{NRS}(1) = 8 - 6 - 0.8 = 3.2\) cm, indicating a 20% return of NRS towards baseline; at the end of week 2: \(\text{NRS}(2) = 8 - 4.8 - 0.64 = 4.9\); etc. \(\epsilon\) is a noise component with variance \(\sigma^2\). Next, probabilities of response and non-response, conditional on ketamine or placebo treatment, were estimated.

The stochastic differential equation was implemented in NONMEM with a Kalman feedback loop (Ljung, 1987). Normal inter-individual variability was assumed to be present on BLN, log-normal on EFF, and distributed within (0–1) via the inverse logit transformation on FAC.

2.4. Pharmacokinetic–pharmacodynamic analysis

A population PK–PD analysis was performed on all responses of R3 that had received ketamine. The NRS data were analyzed using an inhibitory sigmoid-Emax model:

\[
\text{NRS} = \frac{\text{BLN} \cdot (1 + (C_E / C_{50}))^γ}{1 + (C_E / C_{50})^γ},
\]

where \(C_E\) the effect-site ketamine concentration, \(C_{50}\) the ketamine concentration causing 50% effect and \(γ\) a shape parameter.
Treatment onset/offset was modeled by incorporating a rate constant \( k \) (with half-life \( t_{1/2}^k \)), where \( k = \frac{dC_p}{dt}/(C_p - C_E) \) and \( C_p \) is the plasma ketamine concentration. Plasma concentrations were calculated using the individual Bayesian estimates of the pharmacokinetic parameters. BLN was assumed to be normally distributed across the population; \( t_{1/2}^k \), \( C_{50} \) and \( \gamma \) were assumed to be log-normally distributed. Intra-individual error was assumed to be additive and normally distributed.

### 2.5. Statistical analysis

The models as described above were implemented in NONMEM VII (ICON Development Solutions, Ellicott City, MD) (Beal et al., 2009) (see Appendix A). NONMEM VII’s Markov Chain Monte Carlo Bayesian analysis method was used for parameter estimation. This method yields probability distributions of the model parameters from which means, standard errors and 95% confidence intervals (ci) can be obtained. Uninformative priors were used for the inter-individual variability terms. The burn-in samples were tested for convergence (all parameters and objective function over 20 iterations, each 50 iterations apart; \( P < 0.05 \)); 1000 iterations were used to obtain parameter distributions.

### 2.6. Simulation study

Using the pharmacokinetic/pharmacodynamic model parameters derived from the PK/PD analysis (Section 2.4) simulations were performed to get an indication of the ability to induce a persistent analgesic effect with NRS < 3 without the need for a continuous 24-h infusion. To that end multiple daily infusions were simulated. We report two examples: (1) infusion of 35 mg/h for 3 h on five subsequent days from 09:00 till noon in a 70 kg patient (i.e., 0.5 mg/kg per h); (2) infusion of 35 mg/h for 3 h on five subsequent days from 09:00 till noon in a 70 kg patient followed by daily 1-h infusion of 35 mg from 09:00 till 10:00 AM.

### 3. Results

All patients completed the protocol without major side effects. Disease duration ranged from 6 weeks to 32 years. Thirty patients received ketamine (22 women), 30 others placebo (26 women). Between the two treatment groups, patients did not differ with respect to age (46 ± 12 years [mean ± SD]), weight (79 ± 19 kg) or height (172 ± 10 cm). The infusion rate at the end of the treatment period was 20 ± 4 mg/h (per 70 kg). The mean ketamine dose given over 4.2 days was 1568 ± 601 mg (range 533–2637 mg; average...
infusion rate 15.6 ± 6.0 mg/h) with maximum S(+)-ketamine and norketamine concentrations of 248 ± 91 ng/ml (range 81–408 ng/ml) and 280 ± 112 ng/ml (range 68–501 ng/ml), respectively.

3.1. Pharmacokinetic analysis

The PK model, consisting of two ketamine and one norketamine compartment is depicted in Fig. 1. Inspection of the data indicated that the model adequately described the ketamine and norketamine data. Best, median and worst data fits for S(+)-ketamine and corresponding S(+)-norketamine fits are shown in Fig. 2; goodness of fit plots are given in Fig. 3 (A and B: individual predicted versus measured concentration and C and D: weighted residuals versus time). Model parameter estimates together with their 95% confidence intervals are given in Table 1. The fraction $F$ denotes that 36% of ketamine clearance from the central compartment ($CL_{1,ket}$) is metabolized into norketamine. PK model performance was good. For S(+)-ketamine, the median of the PE was 0.2% and the median of the APE 10.1%; for S(+)-norketamine the median PE = −1.6% and median APE = 8.9%.

Upon termination of the 100-h S(+)-ketamine infusion both S(+)-ketamine and S(+)-norketamine showed a rapid decline in concentration (Fig. 2).

3.2. Pharmacodynamic analysis

Population responses of the four groups (including 95% confidence intervals) and goodness of fit plot are given in Fig. 4. Parameter estimates of the autoregressive model are given in Table 2: Parameter EFF(0) equals 4.4 ± 0.29 and FAC = 0.82 ± 0.04 ($t_{1/2,FAC} = \log(\frac{1}{2})/\log(FAC) = 3.5$ weeks or 24.5 days).

![Fig. 3. Individual predicted PK data versus measured data for S(+)-ketamine (A) and S(+)-norketamine (B). (C and D) Weighted residuals, ($Y_{MEAS} - Y_{PRED})/Y_{PRED}$, versus time for S(+)-ketamine concentrations (C) and S(+)-norketamine concentrations (D).](image-url)
No effect (R1 or R2). Twenty-five patients receiving placebo had no treatment effect: 15 showed no change in NRS (R1); 10 showed a reduction in NRS during the treatment week only (R2). Eleven subjects treated with ketamine had no treatment effect: 4 had no change in NRS (R1), 7 showed a reduction in NRS during the treatment week only (R2). The analysis indicates a chance of 0.32 to have no effect when treated with ketamine (non-responders; \( \frac{1}{C_{0}P(E|1)} \), Table 2) and 0.77 when treated with placebo (\( \frac{1}{C_{0}P(E|0)} \), Table 2).

Effect (R3 or R4). Twenty-four subjects had an analgesic response to treatment that persisted beyond the treatment period (R3 or R4): 19 on ketamine, 5 on placebo. Seventeen patients on ketamine did show reduction in NRS that persisted beyond the treatment week but gradually returned to baseline values (R3). Ketamine had a full analgesic effect in just two patients with a NRS of zero during the 11-week observation period (R4, Fig. 4). The chance of having a response to placebo treatment (placebo responder) is 0.23 (\( P(E|0) \), Table 2); the chance of having a response to ketamine treatment is 0.67 (\( P(E|1) \), Table 2). There was a tendency towards an improvement in ketamine effect with shorter disease durations: patients in response groups R1 and R2 had a median duration of disease of 10.2 years (range 138 days to 24 years), R3 8.2 years (range 1–31 years); patients in response groups R4 had the disease for 33 and 103 days.

Fig. 4. Pharmacodynamic (time series) analysis: mean responses (continuous lines) and 95% confidence intervals (broken lines) of the four response groups: (A) Response group 1 (R1), (B) response group 2 (R2), (C) response group 3 (R3) and (D) response group 4 (R4). Patients in groups R1 and R2 are defined as non-responders, patients in R3 and R4 as responders. The grey boxes denote the S(+)-ketamine infusion. (E) Goodness of fit plots: Individual predicted NRS versus measured NRS.
3.3. Pharmacokinetic–pharmacodynamic analysis

The seventeen R3 responses to ketamine treatment (showing a treatment effect in week 0 followed by a slow return to baseline) were incorporated in the PK–PD analysis. The PK–PD model adequately described the data. Examples of data fits (best, median and worst) are given in Fig. 5. All three show that treatment effect persists for several weeks upon the termination of treatment while ketamine concentrations had declined to zero. A goodness of fit plot (individual predicted versus measured VAS data) is given in Fig. 5D. PK–PD parameter estimates together with their 95% confidence intervals are given in Table 3. Most important observations are the $C_{50}$ of 10.5 ng/ml and $t_{1/2k}$ of 11 days.

3.4. Simulation study

The results of the two simulations are given in Fig. 6. In the top panel the 3-h infusion for 5 days and subsequent daily 1-h infusion

<p>| Table 2 |</p>
<table>
<thead>
<tr>
<th>Parameter estimates of the pharmacodynamic (time series) analysis.</th>
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<tr>
<td>Estimate</td>
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<tr>
<td>BLN</td>
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<td>EFF(0)</td>
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<p>| Table 3 |</p>
<table>
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<th>Model parameter estimates of the PK–PD analysis.</th>
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<tr>
<td>Estimate</td>
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<td>Baseline (cm)</td>
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<tr>
<td>$C_{50}$ (ng/ml)</td>
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<tr>
<td>$\gamma$</td>
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<tr>
<td>$t_{1/2k}$ (days)</td>
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<td>$\sigma^2$</td>
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BLN = baseline; EFF(0) = the treatment effect; FAC = the autoregressive coefficient. $P\{E|0\}$ = probability of an effect in the placebo group (R3 or R4), conditional on placebo. $P\{E|1\}$ = probability of an effect in the ketamine group (R3 or R4), conditional on ketamine. $P\{BLN|NE\}$ = probability of R1, conditional on no effect (= R1 + R2). $P\{ZERO|E\}$ = probability of full effect, i.e., VAS going to zero (R4, conditional on presence of sustained effect = (R3 + R4)).
is given (black boxes), together with the plasma (red line) and effect-site (blue line) S(+)-ketamine concentrations. The effect-site concentration is 10.5 ng/ml and equals the S(+)-ketamine C_{50} (Table 3). The effect of the treatment on the pain scores is given in the lower panel for the 12 days treatment (red line) and the 5-day treatment (black line). Ending treatment after 5 days causes a slow increase in pain scores with NRS > 3 occurring within 2 days of the treatment end. The daily 1-h infusion keeps the NRS below 3. Alternative simulations indicate that sparser 1-h infusions (such as every third or fourth day) will cause regular increases of the pain scores above 3. Infusion durations (with 35 mg/h) longer than 1-h are then needed to keep NRS < 3.

4. Discussion

We performed a modeling study on the effect of a 100-h infusion of S(+)-ketamine or placebo on pain relief in sixty patients with complex regional pain syndrome type 1. The analyses yielded the following results: (1) The pharmacokinetic S(+)-ketamine and S(+)-norketamine data were well described with a simple model consisting of a central and one peripheral ketamine compartment and one norketamine compartment. Metabolism of S(+)-ketamine into S(+)-norketamine was modeled by assuming that a part (36%) of the central clearance of ketamine from the central compartment was converted into S(+)-norketamine (factor F in Table 1); (2) Both S(+)-ketamine and S(+)-norketamine concentrations dropped rapidly following termination of the 100-h infusion; (3) Irrespective of the kind of treatment received (ketamine or placebo), some patients responded to treatment (response defined by a reduction in NRS lasting > 1 week) while others did not (absence of response defined by either no reduction in NRS or a reduction lasting no longer than 1 week). In our population, the chance for a ketamine treatment effect was 67%, while the chance for a placebo response was 23%; (4) The C_{50} value for ketamine pain relief (as determined in the PK–PD analysis of data from subjects that showed a ketamine-induced reduction in NRS and a subsequent slow return towards pre-treatment NRS values, R3) was 10.5 ng/ml. The onset/offset half-life was 11 days, indicating that the effect of S(+)-ketamine persisted well beyond the treatment period and dissipated after about 55 days.

4.1. CRPS-1 and the NMDA receptor

CRPS-1 is a chronic pain syndrome of unknown pathophysiology. In contrast to classical neuropathic pain syndromes, there is no proof of clinically evident nerve damage as causative factor (Albazaz et al., 2008). One or more extremities are involved with pain, edema, changes in skin temperature and color and hyperhidrosis as most common symptoms. Chronic pain from CRPS-1 has been associated with multiple alterations in the central nervous system, including, central sensitization at the level of the spinal cord, chemical changes, gray matter volume loss, and altered modulatory mechanisms (such as alterations in diffuse noxious inhibitory control) (Borsook, 2009). Most of these changes may be due to the enhanced neural transmission of excitatory amino acids (Chizh, 2007). Our data indeed implicate sensitized NMDA receptors in the etiology and chronification of CRPS-1 related pain. We observed significant pain relief during administration of the NMDA receptor antagonist S(+)-ketamine that continued well beyond the treatment period in the majority of patients. These effects may be related to desensitization of the NMDA receptors during long-term...
S(+-)ketamine treatment and consequently the effective and continuing blockade of central trafficking of pronociceptive signals lasting for weeks after treatment. A simultaneous reset of central glutamatergic brain circuits involved in pain transmission may also play a role (Borsook, 2009).

4.2. Pharmacodynamic (time series) analysis: responders versus non-responders

We analyzed the dynamics of the NRS data with an autoregressive model without using drug concentration as input to the model; the autoregressive filter (Kalman feedback loop) permitted more accurate estimation of the deterministic parameters and their uncertainties, and consequently, of the outcome versus treatment probabilities (Ljung, 1987). The model assumes an exponential return towards baseline with autoregressive factor FAC. FAC is comparable to parameter k in the PK–PD analysis and was of similar value (FAC = 0.82, indicating a ~20% reduction in pain relief relative to the previous week). The value of FAC corresponds with the value of t½ observed in the PK–PD analysis (t½/FAC = log(½))/log(FAC), 95% CI of t½/FAC = 15–41 days versus 95% CI of t½ = 5–21 days). Note that the large 95% CI for FAC is related to the fact that all data were included in analysis but for the estimation of t½ only the data from response group R3 were included. Furthermore, the t½ may be biased downward due to a somewhat faster onset than offset of effect, even though this was not estimable using our PK/PD model. We used a mixture model to objectively divide the data set into responders and non-responders (response groups R1 and R2 versus R3 and R4, Fig. 4) and estimate the chance for effect/no effect conditional on the treatment given.

We defined patients receiving ketamine who showed pain relief in the treatment week only (patients in group R2) as non-responders. It could be, however, that these patients are fast metabolizers. Ketamine is metabolized in the liver to norketamine via cytochrome P450 enzymes (CYP3A4, CYP2D6 and CYP2C9) (Hijazi and Boulier, 2002). A subanalysis revealed no differences in ketamine clearance among the four response groups. This suggests that the ketamine dosing applied by us was less effective in causing pain relief in the R1 and R2 groups compared to groups R3 and R4. The chance of ketamine treatment failure was about 30%. This could be a dosing effect (higher doses are required in some patients to cause long-lasting pain relief), a duration effect (treatment >100 h may be effective) or related to other causes. Possibly, in non-responders we are dealing with misdiagnosis and hence are treating a non-specific chronic pain disease unresponsive to NMDA receptor blockade (Frölke et al., 2009). Another possibility is the existence of genetic variations in the NMDA receptor subcomponents with lesser sensitivity to ketamine. Genetic variations or single nucleotide polymorphisms are known for various receptor systems and neuromodulators with changed opioid efficacy of carriers of the specific variants (Reyes-Gibby et al., 2007; Lötsch et al., 2009). To the best of our knowledge currently no NMDA receptor variants are known that are associated with reduced ketamine efficacy. The chance of an analgesic response to placebo not different from ketamine treatment was 23%. The placebo analgesic response is a complex reaction involving various psychological phenomena such as expectation, experience, suggestion, attention, and conditioning, all resulting in the activation of analgesic pathways, including the endogenous opioid system (Gracely et al., 1983; Amanzio and Benedetti, 1999). Studies on exogenous μ-opioids treatment indicate the absence of efficacy of these opioids in CRPS-1 (Schwartzmann, 2006). However, it may well be that the opioid-placebo component arose from other opioid subsystems (such as endogenous μ-opioid peptides) with a possible analgesic effect in CRPS-1.

An interesting observation is that in two patients full effect was established (NRS values of 0 reached within 2 weeks of ketamine treatment initiation that lasted the remainder of the study period, Fig. 4D). Both patients had a relatively short disease duration (1 and 3 months). While this could indicate that early treatment of the disease with ketamine will enhance the chance of full recovery, we cannot exclude a normal recovery independent of treatment. Note, however, that none of the patients that received placebo displayed a full effect although some had the disease for just 6 weeks.

4.3. PK–PD model parameters

We used a PK–PD modeling approach to enhance our insight in the effectiveness of the pharmacological treatment in our patient population and obtain useful model parameters to allow the development of treatment regimens aimed at prolonging the analgesic effect and possibly even causing the full resolution of pain symptoms. Furthermore, our current PK–PD analysis of prolonged ketamine treatment allows for the comparison with PK–PD analyses of acute treatment paradigms. The pharmacokinetic model that we applied differs significantly from the model that we used previously to describe the short-term (2-h) infusion of S(+-)ketamine in healthy volunteers, where we required two peripheral ketamine compartments, a series of metabolism compartments, and one peripheral norketamine compartment (Sigtermans et al., 2009b). Our current model with less peripheral compartments seems simpler, possibly due to the fact that due to the sample scheme that was employed fast changes in ketamine concentration could not be uncovered from the current data set. Furthermore, in contrast to our previous study (where we drew arterial blood samples), in the current study we obtained venous samples. Our current model is similar to the pharmacokinetic model used by Herd et al. (2007) to model the metabolism of racemic ketamine into norketamine in a pediatric patient population. The S(+-)norketamine formation clearance (36%, Table 1) corresponds to a value of 29 L h⁻¹ (70 kg)⁻¹. In comparison in children, Herd et al. (2007) estimated a racemic norketamine formation clearance of 12.4 L h⁻¹ (70 kg)⁻¹. When taking into account the differences in weight between our adult patient population and the pediatric population of Herd et al. these values are in close agreement (scaling of our parameter value to a child of 30 kg = 29 · [30/70]⁰⁷⁵ = 15 L h⁻¹).

Another import difference between the current study and previous PK–PD studies is the value estimated for C₅₀. The C₅₀ for chronic pain relief was 10.5 ng/ml versus 373 ng/ml for S(+-)ketamine treatment of acute heat pain (Sigtermans et al., 2009b) and 800 ng/ml for adequate anesthesia with S(+-)ketamine as determined by slowing of the EEG (Schüttler et al., 1987) (potency ratio’s 1:35 and 1:75, respectively). This suggests different mechanisms of action of ketamine, possibly via activation/blockade of different receptor systems, in the production of its different end-points, i.e., chronic pain modulation, dampening of acute nociceptive input, and anesthesia. Indeed, we previously showed that S(+-)-ketamine acute antinociceptive efficacy (using the tail-flick acute pain assay) is greatly reduced in mice lacking the μ-opioid receptor, suggesting that the acute effect of ketamine occur not via the NMDA receptor but rather via the opioid-receptor system (Sarton et al., 2001). The low C₅₀ for pain relief of chronic pain may be of advantage to patients when the efficacy–toxicity balance (i.e., ratio C₅₀ for analgesic effect/C₅₀ for side effect) is greater than one. Our study was not designed to estimate C₅₀ values for any of ketamine’s side effect (including psychomimetic side effects and nausea/vomiting). The current treatment regimen was well accepted by the patients, signifying that serious discomfort from side effects occurs at steady-state plasma concentrations well above those observed in the current study.
In PK–PD modeling studies our parameter $t^\beta$/h (or $t^\beta$/k0) denotes the blood-effect-site equilibration half-life. In acute pain and anesthesia studies the value of $t^\beta$/k0 has values <1 min (Schütter et al., 1987; Herd et al., 2008; Sigtermans et al., 2009b), indicating that these end-points are driven by ketamine’s pharmacokinetics with little or no delay between plasma and effect-site concentrations (and consequently effect). In our study we assume that onset and offset of analgesic effect is indirectly related to the effect-site ketamine concentration (i.e., the concentration at sensitized NMDA receptors expressed on neurons involved in nociception). Our data are best understood by assuming that ketamine initiated a cascade of events that persisted when ketamine molecules were no longer present. The initiating factor may be desensitization of the NMDA receptors, causing a change (reduction) in the flow of nociceptive information from the periphery to the brain and consequently analgesia. $k$ is therefore best considered a disease modulatory parameter. We observed that onset and offset of effect could be modeled by just one parameter rather than requiring a $k$ for onset of effect and $k$ for the offset. We interpret this by assuming that while ketamine modulated the disease process it was not curative and the underlying disease slowly counteracted the beneficiary effect of ketamine with a rate constant very similar of the disease modulatory effect of ketamine. It has been suggested that ketamine dose and duration of exposure determines the clinical outcome in CRPS-1 patients (Borsook, 2009). Single doses seem to provide short-term relief while larger doses given as continuous infusion or repeatedly over multiple days may provide increased duration of pain relief (cf. the simulation study, Fig. 6). Our value of $t^\beta$/h of 11 days suggests that repeated ketamine exposures at 2-week intervals will cause more prolonged reduction of pain scores by at least 50%. We are currently exploring whether this can be achieved in our patients by reducing the infusion duration (i.e., by giving the same amount of drug in a shorter time span). We anticipate that more prolonged or repetitive desensitization of the NMDA receptors may halt disease progress and a possibly initiate a curative process. Our simulation study indicates that prolonged repetitive treatment (such as a daily 1-h infusion, Fig. 6) will keep pain scores below 3. Since we did not include a curative component in the model we remain uninformed whether and if so, at what time point, the ketamine treatment will cause permanent relief of pain.

4.4. Norketamine contribution to ketamine effect?

S(+)-norketamine concentrations were equal or somewhat greater than the S(+)-ketamine concentrations (maximum S(+)-ketamine concentrations = 248 ng/ml versus maximum S(+)- norketamine concentration 280 ng/ml, see also Fig. 2 for examples). Animal data suggest that norketamine contributes to the analgesic effects of ketamine (norketamine potency is about 1/10th to 1/4th of that of ketamine) (Leung and Baillie, 1986; Ebert et al., 1997; Shimoyama et al., 1999). Previously, in human volunteers, we could not determine a significant contribution of norketamine to ketamine’s effect in an acute electrical pain paradigm (Sigtermans et al., 2009b). Recently we assessed the effect of induction of the CYP450 enzymes (using rifampicin treatment) on norketamine metabolism and observed a 300% increase in norketamine metabolism causing a 50% reduction in norketamine plasma concentrations with little or no effect on the ketamine plasma concentrations (unpublished observation). Despite the large reduction in norketamine concentrations no differences in effect (response to heat pain, psychomimetic side effects and sedation) were observed. We argue that norketamine has difficulty passing the blood–brain barrier in humans and hence contributes little to ketamine’s effects when short-term infusions are applied. We cannot exclude some effect of norketamine in the current study as norketamine concentrations remained elevated for more than 4 days. Although we could not determine any contribution of norketamine in the current study using a modeling approach (data not shown), a small contribution to ketamine’s analgesic effect may be present in the data. We relate the inability to model a norketamine effect to the very similar temporal profiles of norketamine and ketamine concentrations over time (see Fig. 2). Taken into account the low relative norketamine potency we believe that a possible contribution of norketamine to the analgesic effect in the current study was small and consequently was without major consequences on our data analysis and conclusions.

4.4.1. Declaration of interest

This study is part of TREND (Trauma RElated Neuronal Dysfunction), a Dutch Consortium that integrates research on epidemiology, assessment technology, pharmacotherapeutics, biomarkers and genetics on Complex Regional Pain Syndrome type 1. The consortium aims to develop concepts on disease mechanisms that occur in response to tissue injury, its assessment and treatment. TREND is supported by a government grant (B3IK03016).

Appendix A. NONMEM code

| $\$PROBLEM CRPS |
| $\$DATA FILE.d |
| $\$INPUT ID DV MDV TRT TIMR |
| $\$CONTR DATA = (TRT) |
| $\$PRIOR NWPRI NTHETA = 7, NETA = 3, NTHP = 0, NETP = 3 |

$\$PRED

GDP = MIXNUM
   BLN = THEKTA(1) + ETA(1)
   EFF = THEKTA(2) + EXP(ETA(2))
   DM1 = THEKTA(3)
   DM2 = DM1/(1 - DM1)
   DM3 = DM2 + ETA(3)
   DM4 = EXP(DM3)
   PAC = DM4/(1 + DM4)
   IF (MIXNUM.EQ.1) EFF = 0
   EXO = 0
   IF (MIXNUM.EQ.2.AND.TIME.GT.0.AND.TIME.LT.1) THEN
       EXO = EFF
   ENDIF
   IF (MIXNUM.EQ.2.AND.TIME.EQ.1) THEN
       EXO = EFF + PAC
   ENDIF
   BLNM = BLN
   IF (MIXNUM.EQ.4.AND.TIME.GT.1) THEN
       BLNM = 0
   ENDIF
   IF (TIME.EQ.0) THEN
       ST = 0
       STUP = 0
       STS = 0
       STSUP = 0
       ELSE
       ST = PAC + STUP + EXO
       STS = PAC + STSUP + EXO
       ENDIF
   YN = BLNM + ST
   YNS = BLNM + STS
   Y = YN + ERR(1)
   STUP = ST + (DV-YN)
   STSUP = STS
References


Ebert B, Mikkelsen S, Thorkildsen C, Borgbjerg FM. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur J Pharmacol 1997;333:99–104.


