Ketamine's second life : Treatment of acute and chronic pain

Sigtermans, M.J.

Chapter 7

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

Albert Dahan, Erik Olofsen, Marnix Sigtermans, Ingeborg Noppers, Marieke Niesters, Martin Bauer & Elise Sarton

accepted in European Journal of Pain 2010

7.1 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.[1–3] This is especially true for neuropathic and inflammatory pain syndromes, including Complex Regional Pain Syndrome type 1 (CRPS1). 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.[4] In the Netherlands the incidence of CRPS-1 is 26:100,000 person years, predominantly affecting women.[5] While a variety of treatments (pharmacological, physiotherapy, spinal cord stimulation) has been applied to this syndrome, randomized controlled trials indicate limited effectiveness.[1,6] One approach to better understand the interaction between a pharmacological intervention and effect is pharmacokinetic-pharmacodynamic (PK-PD) modeling.[7] 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.[6] 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 in the treatment of chronic pain and estimation of a rate constant for effect onset/offset of treatment).

7.2 Methods

Sixty patients diagnosed with CRPS-1 were randomized to receive intravenous S(+)-ketamine (Ketanest S, Pfizer BV, Capelle aan de IJssel, The Netherlands) or placebo (NaCl 0.9%) after approval of the protocol by the local human ethics committee (Commissie Medische Ethiek, POBox 9600, 2300 RC Leiden, The Netherlands). The infusion lasted 100 h from Monday morning 8 AM until Friday noon and was started at 1.2 μg/kg/min (this is 5 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 g.kg-1.min-1 pending absence of unacceptable side effects). The maximal infusion rate that was allowed was 7.2 μg/kg/min (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. 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,[8,9] 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, amitryptiline, 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.[6]

Pharmacokinetic analysis

Two, three- and four compartmental models were used to fit the ketamine concentration data. The best 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 *et al.*[10] so volumes were scaled with WT/70, and clearances with $(WT/70)^{0.75}$. Concentrations were assumed to have constant relative intra-individual error.

Pharmacodynamic analysis

A separate PD 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).
To get an objective indication of a type of response and to allow for the estimation of probabilities of responses belonging to one of the above groups, a mixture model was constructed:

$$\text{NRS(T)} = \text{BLN - EFF(0)} \cdot \text{FAC}^T, \text{ so that}$$
$$\text{EFF(T+1)} = \text{FAC} \cdot \text{EFF(T)} + \epsilon,$$

where T is the week following the treatment (T = 0 is treatment week), EFF(0) = the treatment effect observed at the end of week 0, BLN is baseline (*i.e.*, pretreatment) NRS, and FAC an exponential factor indicating the fraction of NRS at T+1 relative to T. Assume baseline NRS = 8 cm, EFF at week 0 = 6 cm and FAC = 0.8, then at the end of the treatment week: NRS(0) = 8 - 6 = 2 cm; at the end of week 1: NRS(1) = 8 - 6 ·0.8 = 3.2 cm, indicating a 20% return of NRS towards baseline; at the end of week 2: NRS(2) = 8 - 4.8· 0.64 = 4.9 cm; etc.). ϵ is a noise component with variance 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.[11] Normal inter-individual variability was assumed to be present on BLN, lognormal on EFF, and distributed within (0 to 1) via the inverse logit transformation on FAC.

Pharmacokinetic-Pharmacodynamic Analysis

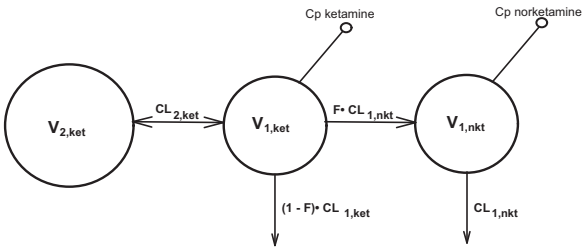
A population PK-PD analysis was performed on all responses of R3 that had received ketamine. The NRS data were analyzed using an inhibitory sigmoid-Emax model:

$$NRS = \frac{BLN}{1+(\frac{C_{ket}}{c_{50}})^{\gamma}},$$

where C_{ket} 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 $t_{1/2}k$). Blood 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 γ were assumed to be log-normally distributed. Intra-individual error was assumed to be normally distributed. Intra-individual error was assumed to be additive and normally distributed.

Statistical analysis

The models as described above were implemented in NONMEM VII (ICON Development Solutions, Ellicott City, MD).[12] 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



(a)

Figure 7.1: Schematic representation of the ketamine-norketamine PK model
Ket is ketamine; nkt is norketamine; Cl is clearance; V volume; F the fraction of $Cl_{1,ket}$ metabolized into norketamine assuming that volumes $V_{1,ket}$ and $V_{1,nkt}$ are equal; Cp is plasma concentration.

(all parameters and objective function over 20 iterations, each with 50 iterations apart; $P < 0.05$); 1000 iterations were used to obtain parameter distributions.

7.3 Results

All patients completed the protocol without major side effects. Disease duration ranged from six weeks to thirty-two 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).

Pharmacokinetic analysis

The final PK model, consisting of two ketamine and one norketamine compartment is depicted in figure 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 figure 2; goodness of fit plots are given in figure 3. Both S(+)-ketamine and S(+)-norketamine showed a rapid decline in concentration upon the termination of the 100-h S(+)-ketamine infusion. 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.

Pharmacodynamic analysis

Population responses of the 4 groups (including 95% confidence intervals) are given in figure 4

No effect (R1 or R2).
Twenty-five patients receiving placebo had no treatment effect (15 showed no change

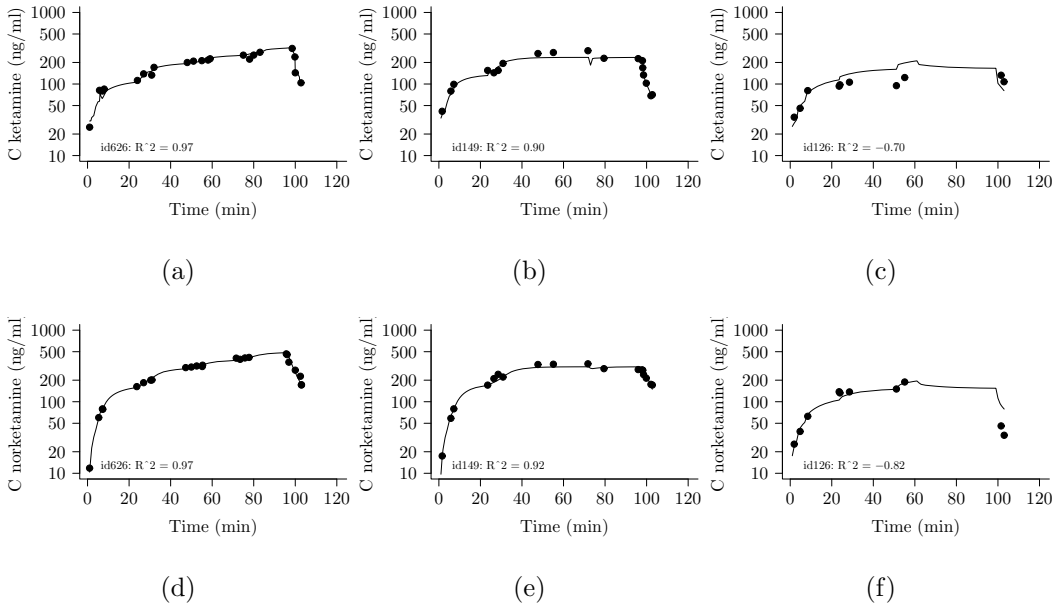


Figure 7.2: PK model fist

Best (a), median (b) and worst (c) PK model fits for ketamine and corresponding norketamine model fits (d – f). Closed circles are measured S(+)-ketamine concentrations, closed squares are measured S(+)-norketamine concentrations, continuous lines data fits.

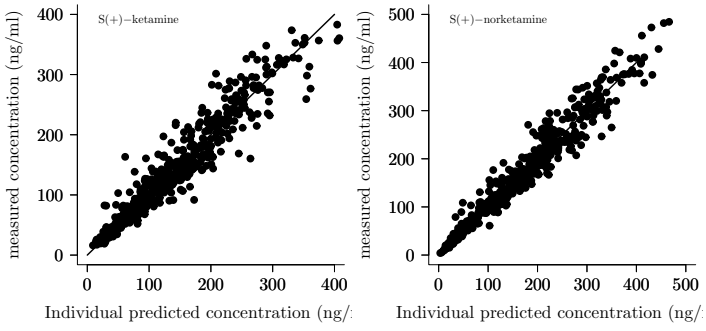


Figure 7.3: Individual predicted PK data versus measured data for S(+)-ketamine (a) and S(+)-norketamine (b).

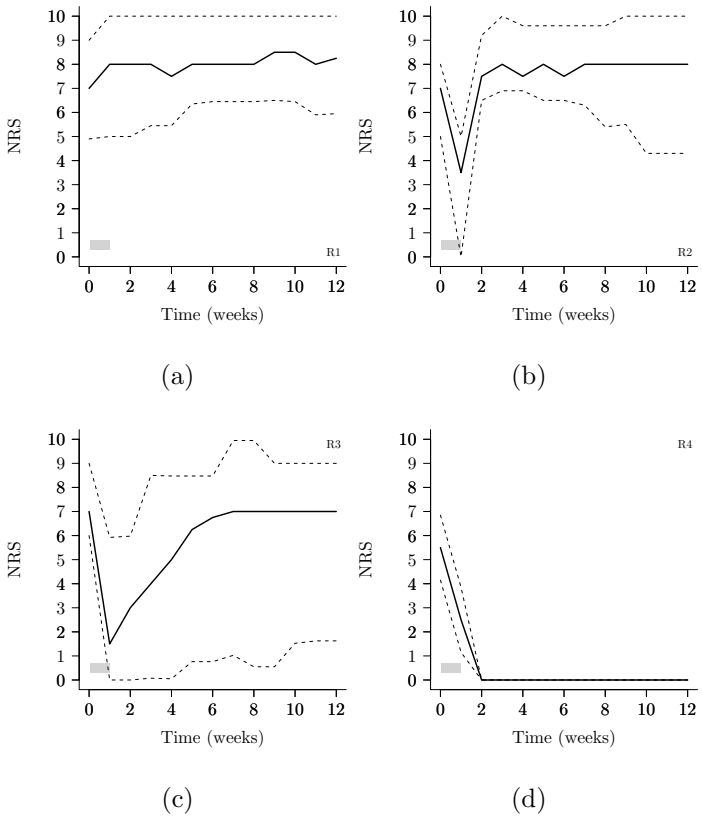


Figure 7.4: Pharmacodynamic analysis

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.

Table 7.1: pharmacokinetic model parameters

	Θ	SE	95% CI	ω^2	SE
$V_1(L)$	53.26	7.60	38.71-69.59	0.477	0.211
$V_2(L)$	507.28	90.69	362.51-717.23	0.753	0.369
$CL_{1,KET}(L/h$ *per 70 kg)*	83.34	5.82	72.36-95.39	0.129	0.042
$CL_2(L/h$ *per 70 kg)*	118.32	19.26	85.62-162.84	0.549	0.224
F	0.36	0.03	0.31-0.41	0.259	0.116
$CL_{NKET}(L/h$ *per 70 kg)*	26.10	2.28	21.78-30.72	0.178	0.064
$\sigma^2{}_{(KET)}$	0.040	0.002	0.035-0.46		
$\sigma^2{}_{(NKET)}$	0.023	0.002	0.020-0.26		

F is the fraction of $CL_{1,KET}$ converted to norketamine assuming that the central compartment volumes of ketamine and norketamine are identical.

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) and 0.78 when treated with placebo.

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, figure 4). The chance of having a response to placebo treatment (placebo responder) is 0.22; the chance of having a response to ketamine treatment is 0.68. 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 - 24 years), R3 8.2 years (range 1 - 31 years); patients in response groups R4 had the disease for 33 and 103 days.

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 figure 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 figure 5D. PK-PD parameter estimates together with their 95% confidence intervals are given in table 2. Most important observations are the C_{50} of 10.5 ng/ml and $t_{1/2}k$ of 11 days.

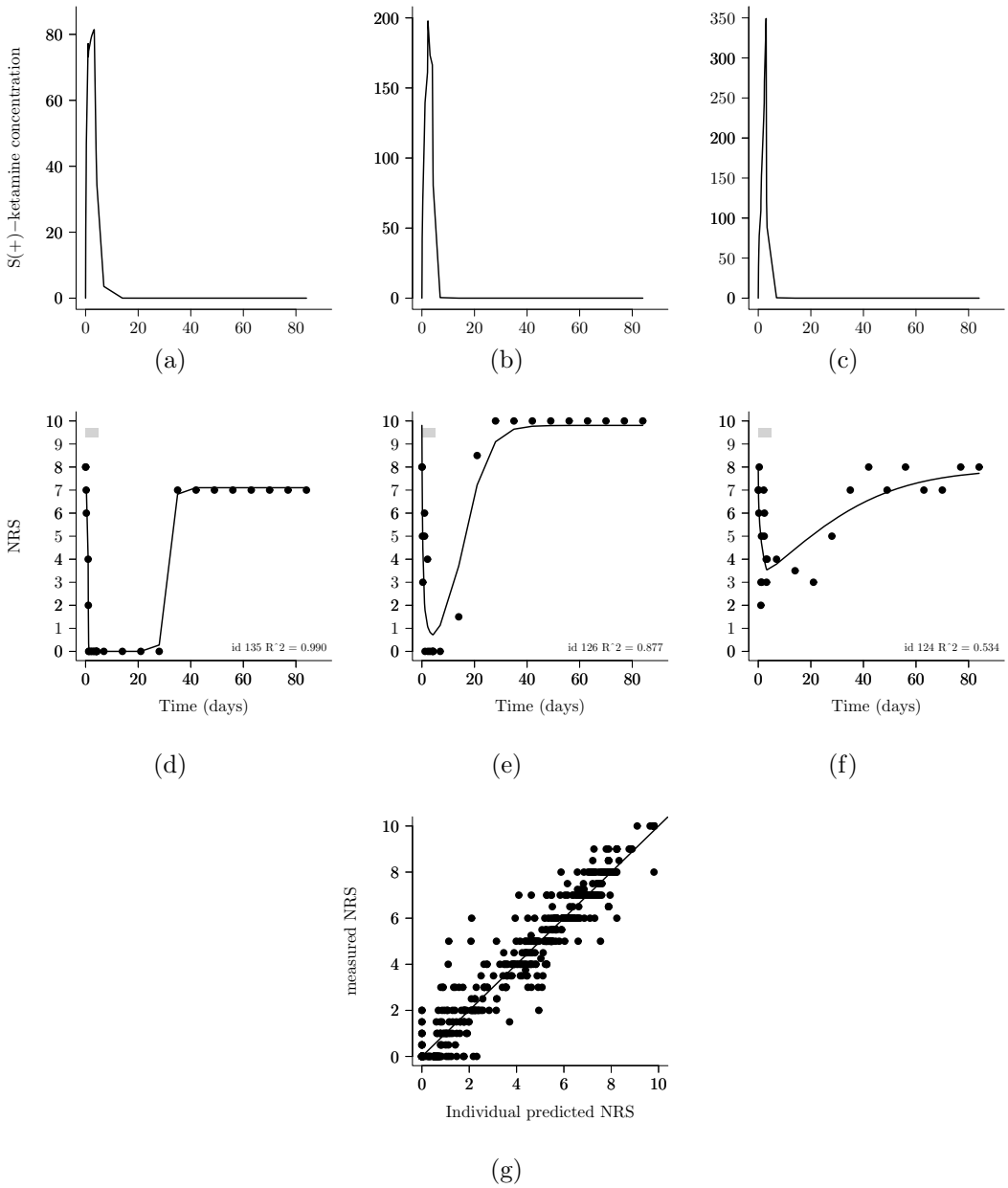


Figure 7.5: PK-PD model fits and goodness of fit plot

Best (a and d), median (b and e) and worst (c and f) PK-PD model fits. In the three top panels the Bayesian estimates of the S(+)-ketamine concentrations are given. In the bottom three panels, measured NRS values are given (closed circles) and data fits (continuous lines). g. Goodness of fit plots. Individual predicted VAS *versus* measured VAS.

Table 7.2: model parameter estimates of the PK-PD analysis

	Θ	SE	95% CI	ω^2	SE
Baseline (cm)	7.02	0.42	6.19 - 7.90	2.62	1.17
C_{50} *(ng/ml)*	10.5	4.77	4.37 - 21.2	2.68	1.40
γ	1.89	0.83	0.79 - 3.84	2.77	1.34
$t_{1/2}k$ *(days)*	10.9	3.97	5.25 - 20.50	1.83	0.81
σ^2 *(NKET)*	0.69	0.05	0.61-0.79		

7.4 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 significant 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 70%, while the chance for a placebo response was 20%; (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.

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.[13] 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).[1] Most of these changes may be due to the enhanced neural transmission of excitatory amino acids.[14] 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.[1]

PD-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.[11] The model assumes an exponential return towards baseline with factor FAC. FAC is comparable to parameter k in the PK-PD analysis and was of similar value (FAC = 82%, indicating a 20% reduction in pain relief relative to the previous week). The value of FAC corresponds with the value of $t_{1/2}$ observed in the PK-PD analysis (95% CI of FAC = 15-41 days versus 95% CI of $t_{1/2}$ = 5 - 21 days; note that the large 95% CI for FAC is related to the fact that all were included in analysis but for the estimation of $t_{1/2}$ only the data from response group R3 were included). 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, figure 4) and estimate the chance for effect/no-effect conditional on the treatment given.

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.[15] 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.[16,17] 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 about 20%. 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.[18,19] Studies on exogenous μ -opioids treatment indicate the absence of efficacy of these opioids in CRPS-1.[20] However, it may well be that the opioid-placebo component arose from other opioid subsystems (such as endogenous κ-opioid peptides) with a possible analgesic effect in CRPS-1.

An interesting observation is that in two patients full recovery was established (NRS values of 0 reached within 2 weeks of ketamine treatment initiation that lasted the remainder of the study period, figure 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 recovery although some had the disease for just 6 weeks.

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.[21] 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.*[22] 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 values of 29 L/h/70 kg. In comparison in children, Herd *et al.*[22] estimated a racemic norketamine formation clearance of 12.4 L/h/70 kg. 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 $= 29 \cdot [30/70]^{0.75} = 15$ L/h).

Another important difference between the current study and previous PK-PD studies is the value estimated for C_{50}. We observed a C_{50} for chronic pain relief of 10.5 ng/ml *versus* 373 ng/ml for S(+)-ketamine treatment of acute heat pain[21] and 800 ng/ml for adequate anesthesia with S(+)-ketamine as determined by slowing of the EEG[23] (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.[24] The low C_{50} for pain relief of chronic pain may be of advantage to patients when the efficacy-toxicity balance (*i.e.*, ratio C_{50} for analgesic effect/C_{50} for side effect) is greater than one. Our study was not designed to estimate C_{50} 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 $t_{1/2}k$ (or $t_{1/2}k_{E0}$) denotes the blood-effect-site equilibration half-life. In acute pain and anesthesia studies the value of $t_{1/2}k_{E0}$ has values < 1 min,[11,21,23] 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 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_{ON} for onset of effect and k_{OFF} 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.[1] 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. Our value of $t_{1/2}k$ 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 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 repetitious desensitization of the NMDA receptors may halt disease progress and a possibly initiate a curative process.

References

1. D. Borsook. Ketamine and chronic pain–going the distance. *Pain*, 145(3):271–272, 2009.

2. J. S. Mogil. Animal models of pain: progress and challenges. *Nat.Rev.Neurosci.*, 10(4):283–294, 2009.

3. I. Kissin. The development of new analgesics over the past 50 years: a lack of real breakthrough drugs. *Anesth.Analg.*, 110(3):780–789, 2010.

4. P. H. Veldman, H. M. Reynen, I. E. Arntz, and R. J. Goris. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet*, 342(8878):1012–1016, 1993.

5. Mos M. de, A. G. de Bruijn, F. J. Huygen, J. P. Dieleman, B. H. Stricker, and M. C. Sturkenboom. The incidence of complex regional pain syndrome: a population-based study. *Pain*, 129(1-2):12–20, 2007.

6. M. J. Sigtermans, J. J. van Hilten, M. C. Bauer, M. S. Arbous, J. Marinus, E. Y. Sarton, and A. Dahan. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain*, 145(3):304–311, 2009.

7. M. Danhof, E. C. de Lange, O. E. la Pasqua, B. A. Ploeger, and R. A. Voskuyl. Mechanism-based pharmacokinetic-pharmacodynamic (pk-pd) modeling in translational drug research. *Trends Pharmacol.Sci.*, 29(4):186–191, 2008.

8. S. Bruehl, R. N. Harden, B. S. Galer, S. Saltz,

M. Bertram, M. Backonja, R. Gayles, N. Rudin, M. K. Bhugra, and M. Stanton-Hicks. External validation of iasp diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. international association for the study of pain. *Pain*, 81(1-2):147–154, 1999.

9. H. Merskey and K. Bogduk. Classification of chronic pain: definitions of chronic pain syndromes and definition of pain terms. 1994.

10. N. H. Holford. A size standard for pharmacokinetics. *Clin.Pharmacokinet.*, 30(5):329–332, 1996.

11. J. Ljung. System identification: Theory for the user. *Prentice Hall, Englewood Cliffs, NJ, USA*, 10 A.D.

12. BL Beal. Nonmem user's guide. 06.

13. R. Albazaz, Y. T. Wong, and S. Homer-Vanniasinkam. Complex regional pain syndrome: a review. *Ann.Vasc.Surg.*, 22(2):297–306, 2008.

14. B. A. Chizh. Low dose ketamine: a therapeutic and research tool to explore n-methyl-d-aspartate (nmda) receptor-mediated plasticity in pain pathways. *J.Psychopharmacol.*, 21(3):259–271, 2007.

15. J. P. Frolke, Rumund A. van, Waardt D. de, R. T. van Dongen, F. P. Klomp, A. L. Verbeek, and Meent H. van de. [complex regional pain syndrome type 1? in 77different diagnosis]. *Ned Tijdschr.Geneeskd.*, 153(12):550–553, 2009.

16. J. Lotsch, G. Geisslinger, and I. Tegeder. Genetic modulation of the pharmacological treatment of pain. *Pharmacol.Ther.*, 124(2):168–184, 2009.

17. C. C. Reyes-Gibby, S. Shete, T. Rakvag, S. V. Bhat, F. Skorpen, E. Bruera, S. Kaasa, and P. Klepstad. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: Oprm1 and comt gene. *Pain*, 130(1-2):25–30, 2007.

18. R. H. Gracely, R. Dubner, P. J. Wolskee, and W. R. Deeter. Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature*, 306(5940):264–265, 1983.

19. M. Amanzio and F. Benedetti. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J.Neurosci.*, 19(1):484–494, 1999.

20. R. J. Schwartzman. New treatments for reflex sympathetic dystrophy. *N.Engl.J.Med.*, 343(9):654–656, 2000.

21. M. Sigtermans, A. Dahan, R. Mooren, M. Bauer, B. Kest, E. Sarton, and E. Olofsen. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology*, 111(4):892–903, 2009.

22. D. W. Herd, B. J. Anderson, and N. H. Holford. Modeling the norketamine metabolite in children and the implications for analgesia. *Paediatr.Anaesth.*, 17(9):831–840, 2007.

23. J. Schuttler, D. R. Stanski, P. F. White, A. J. Trevor, Y. Horai, D. Verotta, and L. B. Sheiner. Pharmacodynamic modeling of the eeg effects of ketamine and its enantiomers in man. *J.Pharmacokinet.Biopharm.*, 15(3):241–253, 1987.

24. E. Sarton, L. J. Teppema, C. Olievier, D. Nieuwenhuijs, H. W. Matthes, B. L. Kieffer, and A. Dahan. The involvement of the mu-opioid receptor in ketamine-induced respiratory depression and antinociception. *Anesth.Analg.*, 93(6):1495–500, table, 2001.