Safety-efficacy balance of S-ketamine and S-norketamine in acute and chronic pain

Noppers, I.M.

Chapter 3

Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients:
A report of 3 cases

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Pain, in press

Introduction

It is well established that the *N*-methyl-D-aspartate receptor (NMDAR) plays an important role in the etiology and duration of chronic pain.[1,2,3,4] Chronic pain activates and upregulates the NMDAR in the dorsal horn of the spinal cord, which causes enhanced signal transmission in the pain circuitry and leads to chronic pain, often coupled with allodynia and hyperalgesia.[1,2,3] Consequently, drugs that block the NMDAR are able to relieve chronic pain and possibly modulate the underlying disease process.[1,2,3,4] The most potent NMDAR antagonist currently available is ketamine, and the number of studies on the efficacy of ketamine increases rapidly. Since 1992 there are 38 published randomized controlled trials on ketamine use in chronic (non-cancer) pain patients and even more open-label and case studies.[4] Most of the published randomized controlled trials (36/38) are of poor-to-moderate quality. Despite the absence of good quality studies, ketamine treatment seems to get a definite place in the treatment of chronic pain in clinical practice.[4]

The use of ketamine has raised the concern for toxicity.[5] Animal studies indicate that ketamine use is associated with neurotoxicity and learning disabilities, while human studies indicate abuse potential and a high frequency of psychotropic side effects. Case reports on the side effects and toxicity of the recreational abuse of ketamine indicate a pattern of renal and liver toxicity.[6,7,8] During the course of a study on repeated administrations of ketamine for treatment of chronic pain in patients with complex regional pain syndrome type 1 (CRPS-1), we encountered hepatotoxicity in a subset of patients that received 2 100-hour infusions of S-ketamine at a 16-day interval. Six subjects were enrolled in that study arm and liver damage was observed in 3 of them. This prompted us to end the trial prematurely. Liver damage is considered a rare side effect of ketamine use, but since repeated dosing is often necessary, we believe that awareness of this side effect is needed. We therefore present the course of events of the 6 subjects enrolled in the 16-day interval study arm.

Methods

The patients presented were involved in a study registered in the Netherlands Trial Register (www.trialregister.nl) under number NTR1550. This pilot study was aimed at generating exploratory data on the effect of two 5-day (i.e., 100 h) ketamine treatments (treatment 1 in week 1, treatment 2 in week 4) on pain relief in CRPS-1 patients.

Patients

Patients eligible for the study were those referred to our outpatient pain clinic and who were diagnosed with CRPS-1, as based on the International Association for the Study of Pain CRPS-1 criteria[9], and who had pain scores of 5 or higher (on a numerical rating scale (NRS) from 0 to 10, where 0 = no pain and 10 = worst pain). Exclusion criteria included age < 18 years, inability to give informed consent, serious medical disease (e.g., cardiovascular, renal, or liver disease), use of strong opioids or baclofen, pregnancy/lactation, and history of psychosis. Patients were asked not to change their pain medication from the start of the study until completion of follow-up.

Trial design

The study design was single blind. Patients were admitted twice for 5 days and randomly allocated to 1 of 3 groups: Group 1 was admitted in weeks 1 and 4 and received ketamine on both occasions (i.e., they had a 16-day ketamine-free interlude); Groups 2 and 3 were admitted in weeks 1 and 13 and received ketamine on both occasions (Group 2) or midazolam on the first occasion and ketamine on the second (Group 3). Follow-up was performed during the 12 weeks after the second admission. Since the focus of this report is on the side effects observed in the Group 1 subset of patients, we restrict our presentation to these patients.

Treatment

S-ketamine (Ketanest S, Pfizer BV, Capelle aan de IJssel, The Netherlands) was administered continuously by intravenous route for 5 days according to an infusion scheme of Sigtermans et al.[10] On day 1, infusion started at 8 am at 1.2 μg/kg/min. Three times a day (at 8 am, noon, and 4 pm), the infusion rate could be increased in steps of 0.6 μg/kg/min until a maximum infusion rate of 7.2 μg/kg/min was reached. When the patient reached a pain rating of zero, the infusion rate was not further changed. In case of severe side effects, the infusion rate was lowered in steps of 0.6 μg/kg/min and later increased again if possible. On day 5, at noon, the infusion ended. In case of nausea, 10 mg oral domperidone could be given, with a maximum of 40 mg per day.

Measurements

The primary outcome measure of the study was pain relief as measured by the 10-point NRS ranging from 0 (no pain) to 10 (worst pain), measured 3 times daily (8 am, 12 pm, and 4 pm) during treatment, and weekly in between treatments and during follow-up. Secondary outcome parameters were psychotropic side effects, nausea, and headache, all scored on a range from 0 (not present) to 10 (maximal presence). Liver enzymes (alkaline phosphatase (ALP; reference values

40-120 U/L), alanine transaminase (ALT; reference values 5-34 U/L), aspartate transaminase (AST; reference values 5-30 U/L), total bilirubin (TBIL; reference values 0-17 U/L), γ-glutamyltransferase (γGT; reference values 5-40 U/L)) were measured during ketamine treatment (in weeks 1 and 4) on days 1 (before the start of drug infusion), 3, and 5. In case of liver enzyme elevation, the frequency of testing increased to twice daily. Heart rate, blood pressure, and tympanic temperature were obtained 3 times per day.

Statistics

The total number of subjects in this pilot study was arbitrarily set at 30 (10 per group). No comparative analysis was planned, and the data are presented in a descriptive manner only.

Results

Patient admissions took place between December 2008 and February 2010. The inclusion of patients in the study was ended prematurely after 13 subjects had been admitted. Five of the 6 subjects randomized to Group 1 developed side effects: one developed severe hypertension and another psychotropic side effects during their first exposure to S-ketamine, and 3 developed elevated liver enzymes prior to or during their second exposure to S-ketamine. The development of hepatotoxicity was such that we decided that continuation of the trial was unjustifiable. See Figure 1 for a flow chart of the study. None of the subjects randomized to Groups 2 (n = 2) and 3 (n = 5) developed severe side effects. In Table 1, the characteristics of patients randomized to Group 1 are given.

Patient A: a 65-year-old woman with CRPS in her left foot

During treatment in week 1, pain score reduced from 7 to 2 on day 2 of the ketamine infusion. Due to the development of severe psychotropic side effects, nausea, and dizziness, the infusion was reduced to 2.1 μg/kg/min on day 2. At this infusion rate, side effects were bearable. An increase in infusion rate was not possible, and the pain score increased to 5 at the end of the infusion. No increase in liver enzymes was detected in treatment week 1 (Figure 2). Upon admission in week 4, pain had returned to prestudy baseline level and on day 2 of the treatment, similar side effects occurred as had been seen in week 1 (ketamine infusion rate 2.7 μg/kg/min, pain score 2). After 72 h of ketamine infusion, the patient developed an itching rash on legs, abdomen, back, and upper arms, combined with an increase in tympanic temperature to 38.3 °C. The blood tests performed on day 3 revealed elevated liver enzymes (see Figure 2; ALP, ALT, AST, TBIL, and γGT exceeded the upper reference values). A diagnosis of drug-

induced liver injury (DILI) was made and the ketamine infusion was terminated (total amount of ketamine infused at that time was 1.3 g). Also, all other medication was stopped. Jaundice and tenderness or enlargement of the liver were absent on physical examination. No further abnormalities were observed in blood hematology or chemistry, apart from a small increase in eosinophilic and neutrophilic leukocytes (to 8% and 77%, respectively). The patient received topical corticosteroid and oral clemastine to treat the pruritus. Liver enzymes decreased upon termination of the ketamine infusion, except for ALP and γGT, which increased for another day. The patient was discharged on day 5 with an NRS of 3. After discharge the rash slowly improved, disappearing completely within 2 weeks. Liver enzymes returned to normal within 1 month, except for γGT, which normalized within 2 months. The patient continued to experience a lack of energy following discharge for 6 months. The pain score returned to baseline 5 weeks after discharge.

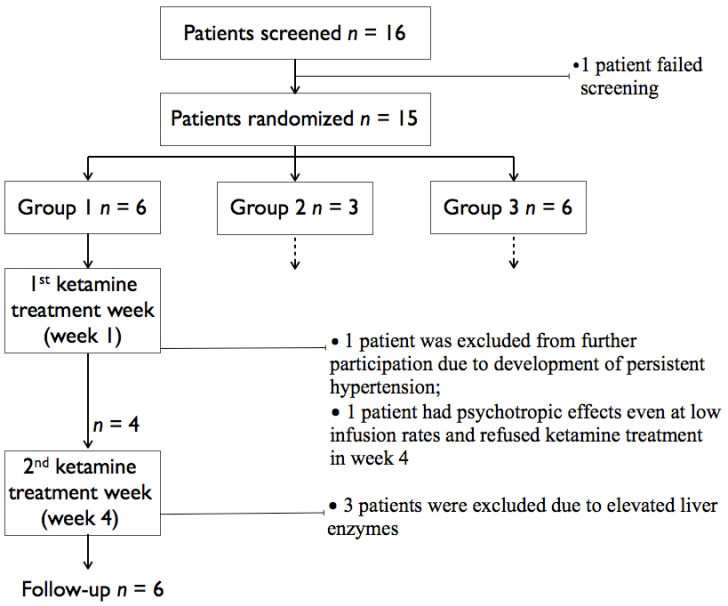

Figure 1 Flow chart of Group I of the study at the time of study termination.

Patient B: a 53-year-old woman with CRPS in her right arm

Ketamine produced a reduction in CRPS pain score from 8 to 2 on treatment day 2. On day 3 the patient was pain free. On day 4 she experienced severe psychotropic side effects: fearsome hallucinations and a panic attack. She refused further treatment and was discharged with a pain score of 4. Pain relief lasted for another 13 weeks. No increase in liver enzymes was detected during ketamine treatment.

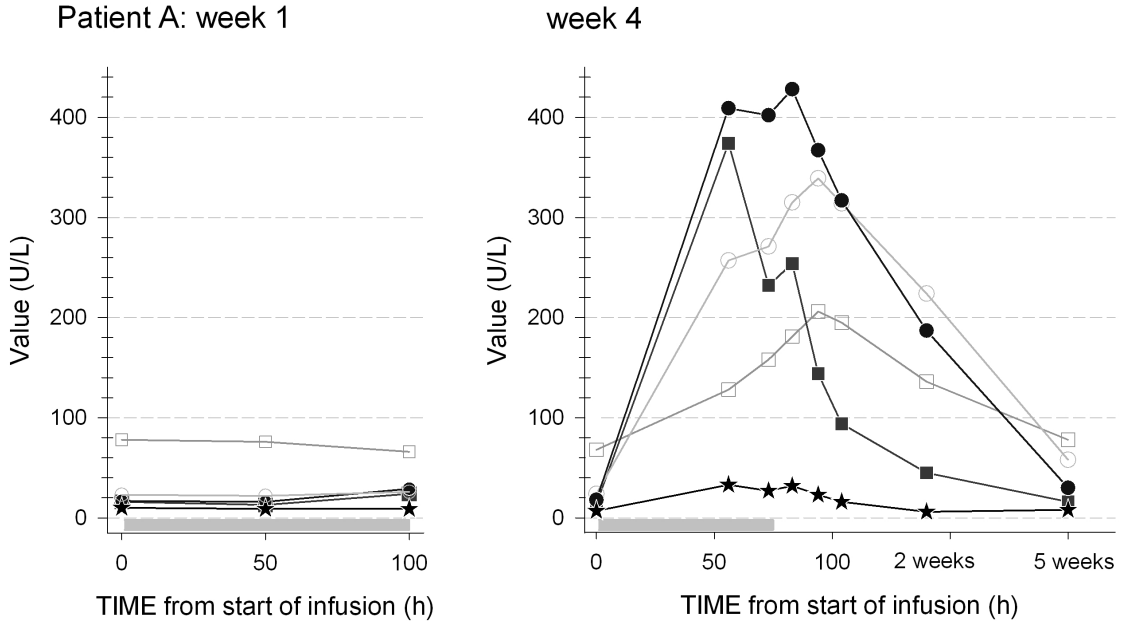

Figure 2 Serum liver enzymes in the first (**left**) and second (**right**) S-ketamine treatment week (= study week 4) of patient A. Alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, and γ-glutamyltransferase exceeded the upper reference values. Reference values: alkaline phosphatase (open square) 40-120 U/L, alanine transaminase (closed circle) 5-34 U/L, aspartate transaminase (closed square) 5-30 U/L, total bilirubin (black star) 0-17 U/L, and γ-glutamyltransferase (open circle) 5-40 U/L. The gray bar indicates the ketamine infusion.

Patient C: a 39-year-old woman with CRPS in both arms

In treatment week 1 there was a slow and modest reduction in CRPS pain score from 9 to 6 on day 3. She developed a gradual increase in mean arterial blood pressure from 93 to 135 mmHg on day 3. Decreasing the infusion rate did not lower the blood pressure and the treatment was terminated on day 4 (pain score 6, mean arterial pressure 130 mmHg). The decision was made by the investigators and patient to not participate in the second ketamine session. The high blood pressure was successfully treated with antihypertensive medication that is continued to date. No increase in liver enzymes was detected during ketamine treatment.

Patient D: a 20-year-old woman with CRPS of the left leg

Upon admission in week 1, CRPS pain score was 9. The ketamine infusion rate was increased to the maximum dose without any effect on the pain score. The patient experienced no side effects. On day 5 the patient was discharged with pain score 9. A similar course was observed during treatment in week 4. The pain score was 9 upon discharge and remained between 8 and 9 during the follow-up period. No increase in any of the liver enzymes was detected during ketamine treatment in weeks 1 and 4.

Table 1 Patient characteristics, NRS and ketamine treatment.

Patient	Age (y); Sex	BMI (kg/m²)	Cause of CRPS	Duration of CRPS (months)	Affected limbs	Pain medication at admission	NRS at baseline	Ketamine amount in week 1 (mg)	Ketamine amount in week 4 (mg)
A	65; f	38	Surgery	74	Left leg	Tramadol 3 dd 50 mg Paracetamol/codeine od	7	1575	1301
B	53; f	34	Surgery	30	Both arms	Ibuprofen 600 mg od	8	1220	–
C	39; f	32	i.v. line placement	144	Right arm	Tramadol 3 dd 100 mg Gabapentin 4 dd 600 mg Ibuprofen 2 dd 800 mg Oral contraceptive	9	1288	–
D	20; f	20	Contusion	78	Left leg	Tramadol 1 dd 150 mg Tramadol/paracetamol 4 dd 37.5/325 mg Amitriptyline 1 dd 20 mg	9	1412	1416
E	48; f	29	Fracture	105	Right leg	Naproxen 2 dd 500 mg Cannabis tea 1–2/wk	6	2084	794
F	46; m	30	Fracture	11	Left arm	-	8	3297	88

BMI = body mass index; **CRPS** = complex regional pain syndrome; **NRS** = numerical rating scale; **i.v.** = intravenous; **od** = on demand; **dd** = times daily.

Patient E: a 48-year-old woman with CRPS of the right foot

Ketamine induced gradual pain relief, with CRPS pain NRS 6 to 0 on day 4. During treatment the patient experienced various side effects, including psychotropic effects, sedation, dizziness, and nausea. No increase in liver enzymes was detected during the first ketamine treatment week. Upon the start of treatment in week 4, CRPS pain score was 3. Within 1 day of ketamine treatment, the pain score was reduced to 1. Side effects were again present, but they seemed of lesser intensity compared to the first admission. For nausea, domperidone was given. Routine blood screening on day 3 revealed elevated liver enzymes (Figure 3; ALP, ALT, AST, TBIL, and γGT exceeded the upper reference values). The ketamine infusion was ended on that same day (total dose given, 800 mg). The patient had no fever, jaundice, abdominal tenderness, or enlargement of the liver.

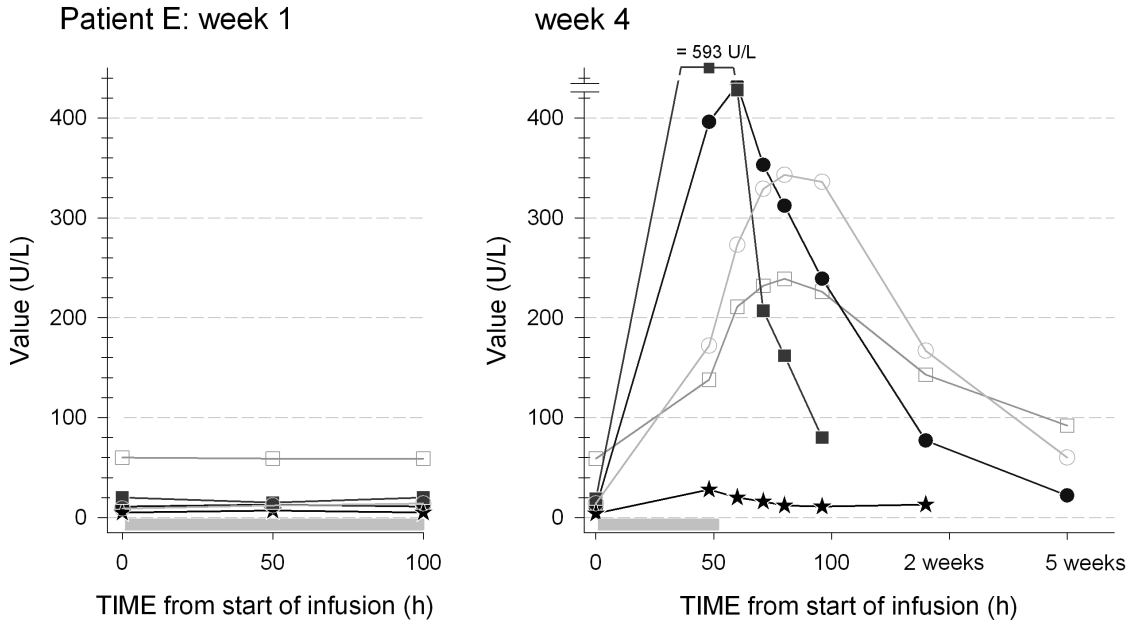

Figure 3 Serum liver enzymes in the first (**left**) and second (**right**) S-ketamine treatment week (= study week 4) of patient E. Alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, and γ-glutamyltransferase exceeded the upper reference values (for reference values see Figure 2 legend). The gray bar indicates the ketamine infusion.

The following tests were performed: renal function; clotting time; serum concentrations of ammonia and lactate; serology for hepatitis A, B, and C; cytomegalovirus; Epstein-Barr virus; and antinuclear, antimitochondrial, and anti-smooth muscle antibodies. All tests were normal or negative except for the antinuclear antibody, which was weakly positive. An ultrasound of the liver, bile ducts, and related vasculature showed no abnormalities. On day 4 the patient developed a severe itch of both feet and petechiae. The CRPS seemed to flare up

with edema of the right foot and an increase in pain score to 6. The patient was discharged on day 5, after which liver enzymes slowly decreased and the itch and petechiae disappeared over a course of days to weeks. The liver enzymes normalized within 2 months.

Patient F: a 46-year-old man with CRPS of the left arm

Before treatment, the CRPS pain score was 8. Upon ketamine infusion, a slow decline in pain score occurred with no side effects apart from mild sedation. During the course of the week, the patient experienced various episodes of sub-febrile temperature (37.9 °C) without any signs of illness, infection, or allergy. At discharge, the pain score was 4. Upon admission in week 4, the CRPS pain score had increased to 7. The ketamine treatment was started, but terminated on the same day after 6 h of infusion, when the results of the blood screening became available: ALT was elevated to 77 U/L (normal range 5-34 U/L) and γGT was elevated to 267 U/L (5-40 U/L). The other enzymes remained within the range of normal. A second sample 8 h after the initiation of treatment gave similar values. The patient denied the use of alcohol, intake of any medication, or any episodes of epigastric pain in the period prior to his second admission. Blood hematology tests revealed the absence of gallstones or signs of infection. Since we discontinued ketamine treatment, the patient refused any follow-up blood measurements. Two additional blood samples were taken 1 week and 4 months later, by the patient's family doctor: γGT remained elevated (92 U/L) in the first sample but was normalized in the second.

The course of pain relief and ketamine infusion scheme, an average plot of the pain scores and ketamine infusion rates is given in Figure 4 for 5 patients of Group 1 (data from patient D are excluded in this graph). Since the study was single blind and not placebo-controlled, these data do not constitute efficacy data, but do give an impression of the effect of treatment on pain scores.

Discussion

Ketamine is increasingly used for the treatment of chronic pain. Data from recent trials suggest that prolonged or repetitive administrations of this agent are needed to induce long-term pain relief, that is, pain relief outlasting the treatment period for a period longer than 48 h.[4] In a previous study we showed that a single continuous 100-hour infusion of ketamine produces the relief of CRPS pain for up to 11 weeks, compared to placebo.[10] This is a somewhat disappointing effect and prompted us to examine the effect of a second 100-hour infusion period on pain relief in CRPS-1 patients.

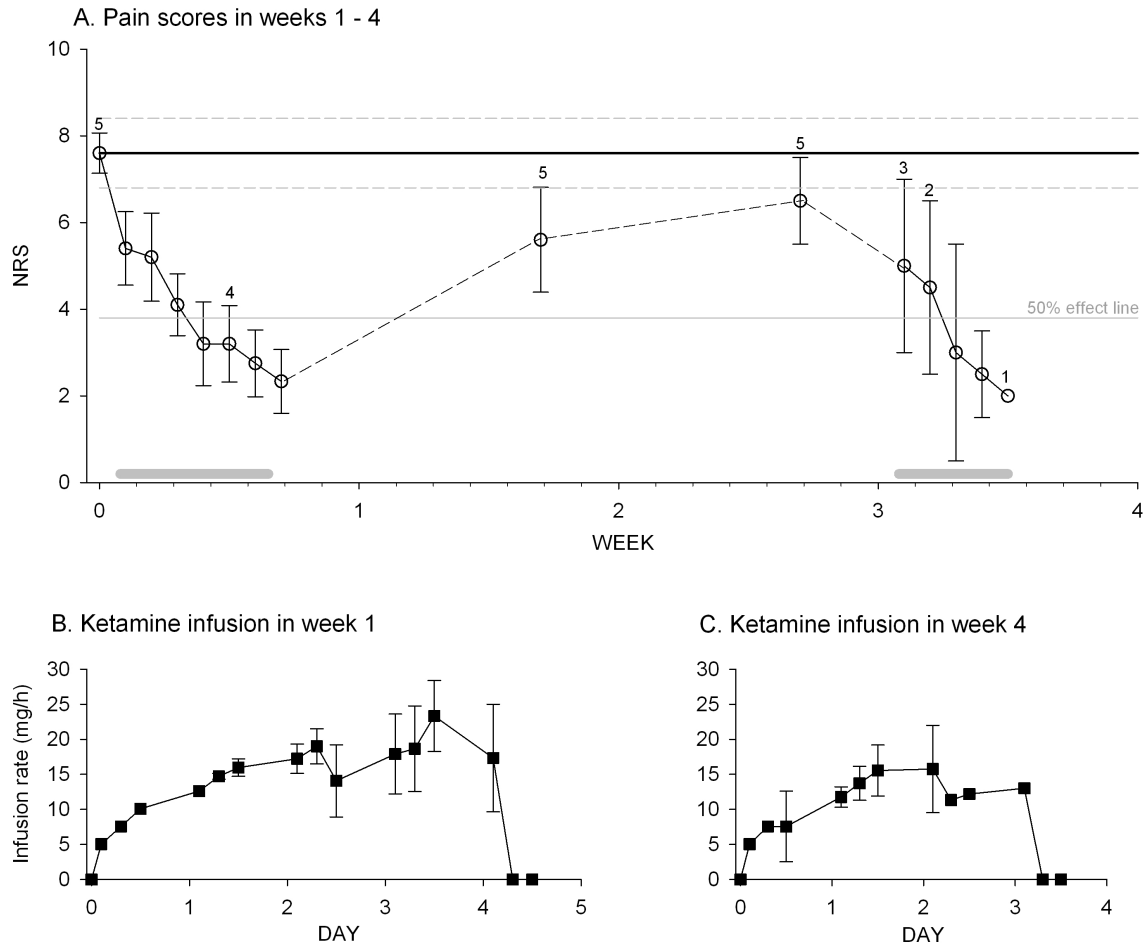

Figure 4 Pain data and infusion rates of 5 subjects showing an analgesic response during treatment with ketamine (given in a single-blind fashion). **A** Numerical rating scores from week 1 to the end of week 4. The continuous black line is the pretreatment baseline mean numerical rating score ± 95% confidence interval (dashed gray lines); the continuous gray line is the 50% effect line; the gray bars indicate the ketamine infusion. The numbers indicate the number of patients from which the pain data was obtained. **B** Ketamine infusion rates (mg/h) for the first treatment week (week 1). **C** Ketamine infusion rates for the second treatment week (week 4) Values are mean ± SEM.

A pilot study was designed to explore possible time frames for ketamine re-administration (4 weeks versus 13 weeks). Apart from the expected psychotropic and hypertensive side effects, we encountered a problem that so far was considered a rare side effect of ketamine administration -elevation of serum liver enzymes- at a relatively high frequency. In 3 patients in study Group 1, the increase in liver enzymes was detected just prior or during a second ketamine administration, 16 days after an initial 100-hour treatment. We relate the cause of elevated liver enzymes to ketamine-induced hepatotoxicity in patients A and E, as there was an evident chronological relation between the ketamine infusion and the development and resolution of the liver injury (e.g., liver enzymes declined

rapidly upon termination of treatment). The cause of the liver enzyme elevation in patient F is less clear and is possibly related to the ketamine treatment.

We made the decision to end the trial, as we argued that repetitive long-term ketamine infusions within a short time frame is a risk factor for liver cell damage and we therefore concluded that our study design (in Group 1 patients) is not acceptable. These data contrast findings in our previous study; patients in the Sigtermans et al. trial received a single 100-hour infusion of ketamine with an average ketamine dose of 2.5 g (range 1.7-3.3 g) without any signs of liver toxicity or side effects beyond the duration of treatment.[10] Some of the patients in the current study used co-medication that might have had an effect on liver function.

Ketamine-induced liver injury

The first reports on an association between ketamine and liver injury date from 1979-1980. In the isolated rat hepatocyte, supraclinical doses of ketamine inhibited gluconeogenesis, and urea formation from alanine caused a reduction in adenosine triphosphate concentration and a dose-dependent leakage of L-lactate dehyrogenase.[11] Dundee et al. described a higher incidence of significant elevations in liver enzyme levels in patients receiving 3-4 mg/kg ketamine for induction and maintenance of general anesthesia compared to "standard" techniques (involving halothane and thiopentone).[12] Fourteen (of 34) patients receiving ketamine and 7 (of 34) receiving standard treatment had signs of liver injury.

Most studies on the use of ketamine for chronic pain treatment either did not measure liver enzymes or found an absence of changes in plasma liver enzymes.[10,13,14] For example, in 30 patients receiving a 100-hour continuous infusion of ketamine (infusion rate between 10 and 20 mg/kg), no effect on liver enzymes was observed during the ketamine treatment period, but no measurements were made thereafter.[10] Sporadic reports of liver injury do appear.[15-18] For example, in refractory CRPS patients receiving ketamine in anesthetic dosages for 5 days, modest elevations in liver enzymes were noted in 16 (of 20) patients on the last days of treatment.[18] Following treatment, the enzymes returned to reference values within 10 to 14 days. In another study, low-dose ketamine given to CRPS patients caused elevated liver enzymes in 4 (of 33) patients during a first treatment period (duration of treatment ranged from 4 to 20 days; ketamine infusion rate 10-50 mg/h).[16] One of these patients who required additional treatments 3 months later developed immediate elevations of his liver-enzyme profile during 2 more treatment attempts. More frequent incidence of liver damage is observed following frequent recreational ketamine abuse.[6-8,19,20] These patients often present with kidney injury, elevated liver enzymes, and bladder dysfunction. Some of these patients have epigastric pain, but in most

cases the elevated liver enzymes were discovered upon blood examination when the patients came in for urinary tract symptoms.[19,20]

All of the above studies that reported liver injury in response to ketamine treatment used a racemic ketamine mixture. In our study we administered the S(+)-enantiomer indicating that the enantioselective use of ketamine will not protect the patient for possible liver injury.

Drug-induced liver injury (DILI)

Drug-induced liver injury is unpredictable (i.e., not dose related, and difficult to reproduce in animal models) and is considered to have a rare incidence.[21] Various forms have been described (hepatitis, cholestasis, cirrhosis, granulomas, steatosis, neoplasms, vascular). DILI may have immune-mediated (allergic) and non-immune-mediated (non-allergic) features. In the allergic form, the innate immune system responds to the drug or its metabolite as if it was a toxic foreign body or infectious organism causing a sterile inflammatory response. In the non-allergic form, mitochondrial impairment, oxidative stress, and cellular adaptation failure are causative factors. Allergic DILI has a latency period of 1-6 weeks, with a high incidence of fever, rash, and eosinophilia, is not dose related, and recurs upon drug re-challenge. Non-allergic DILI has a latency of 1 month to 1 year and is possibly dose related, while the occurrence of rash, fever, and eosinophilia is uncommon.

On the basis of the liver enzyme level, DILI is classified into hepatitis, cholestasis, or a mixed pattern.[21] DILI is defined as hepatitis when: ALT ≥ 3 ULN (where ULN = upper limit of the normal value) and (ALT/ULN)/(ALP/ULN) ≥ 5; as cholestatic when ALP ≥ 2 ULN and (ALT/ULN)/(ALP/ULN) ≤ 2; and mixed when 2 < (ALT/ULN)/(ALP/ULN) < 5. In severe cases of DILI, the patient may develop acute liver failure defined by coagulopathy (international normalized ratio ≥ 1.5) and hepatic encephalopathy occurring in the 6 months following the onset of DILI. On the basis of these definitions, the clinical features, and additional laboratory tests, we diagnosed patients A and E as having ketamine-induced hepatitis of the allergic form. While the cause of elevated enzymes in patient F is likely to be the administration of ketamine in week 1, the nature of the hepatotoxicity remains unknown. For patients A and E, it remains unclear whether co-medication played an additional role in the development of DILI. For example, patient A used paracetamol (acetaminophen). While this drug is associated with non-allergic DILI, it may have enhanced ketamine-induced liver injury. In a rat study, a synergistic hepatotoxic effect (increases in ALT and AST) was observed for ketamine and the solvent carbon tetrachloride.[22] A similar mechanism may possibly occur for paracetamol and ketamine. Further studies are needed to study paracetamol ketamine interaction on liver function. Also,

contraceptive pills are associated with elevated liver enzymes. Only patient C used these, without liver enzyme elevations during the ketamine infusions.

Warning signs for the development of DILI include abdominal pain, nausea/vomiting, and jaundice.[21] However, during ketamine treatment, nausea and vomiting may occur from ketamine itself, and abdominal pain may be absent due to analgesia. We therefore advise frequent testing during long-term ketamine treatment, especially when repeated ketamine infusions are given within short time frames. Treatment of ketamine-induced DILI is by prompt discontinuation of the exposure to ketamine and supportive/symptomatic treatment. In severe allergic hepatitis with no improvement upon drug removal, a 1-week treatment with steroids may be attempted, although proof for efficacy is limited at present.[23]

In summary, a study designed to explore the effect of repeated 100-hour ketamine infusions on pain relief in CRPS patients was ended prematurely due to the development of ketamine-induced hepatitis of allergic nature in 2 patients. In a third patient, liver injury was observed, although its origin cannot be confirmed with certainty. All affected patients (n = 3) received 2 ketamine exposures within 4 weeks' time, while patients receiving ketamine at a wider time interval (12 weeks, n = 2) had no signs of liver injury. Liver enzyme levels returned to normal in all patients within 2 months following the discontinuation of treatment. Patients that receive long-term or repetitive ketamine infusions for the treatment of chronic pain should receive regular monitoring of blood pressure and psychotropic side effects. Furthermore, as suggested by our current report of 3 cases, regular measurements of liver function are strongly advisable. Whether ketamine treatment should be extended to chronic pain patients other than CRPS type 1 requires further study, with the need for high-quality randomized trials, not only focusing on analgesic efficacy, but also carefully monitoring the myriad of short- and long-term side effects linked to ketamine treatment.

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