Complex regional pain syndrome related movement disorders: studies on pathophysiology and therapy.
Munts, A.G.

Citation

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Note: To cite this publication please use the final published version (if applicable).
Chapter 8

Intrathecal glycine for pain and dystonia in complex regional pain syndrome

Alexander G. Munts, MD,1 Anton A. van der Plas, MD,1 Joan H. Voormolen, MD,2 Johan Marinus, PhD,1 Irene M. Teepe-Twiss, PharmD, PhD,3 Willem Onkenhout, PhD,4 Joop M. van Gerven, MD, PhD,1,5 and Jacobus J. van Hilten, MD, PhD,1

1Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands
2Department of Neurosurgery, Leiden University Medical Centre
3Department of Pharmacy, Leiden University Medical Centre
4Department of Clinical Chemistry, Leiden University Medical Centre
5Centre for Human Drug Research, Leiden, The Netherlands

Published in Pain (2009;146:199-204)
Abstract
Since glycnergic neurotransmission plays an important inhibitory role in the processing of sensory and motor information, intrathecal glycine (ITG) administration may be a potential therapy for both pain and movement disorders in patients with complex regional pain syndrome (CRPS). Aims of the current study, which is the first report on ITG in humans, were to evaluate its safety and efficacy. ITG treatment during 4 weeks was studied in CRPS patients with dystonia in the period before they received intrathecal baclofen treatment. Twenty patients were assessed and after exclusion of one patient, the remaining 19 patients were randomised in a double-blind placebo-controlled crossover study. Safety was assessed by clinical evaluation, blood examinations and electrocardiograms. Efficacy measures involved pain (numeric rating scale, McGill pain questionnaire), movement disorders (Burke-Fahn-Marsden dystonia rating scale, unified myoclonus rating scale, tremor research group rating scale), activity (Radboud skills questionnaire, walking ability questionnaire), and a clinical global impression (CGI) and patient's global impression score (PGI). Treatment-emergent adverse events were generally mild to moderate and not different from placebo treatment. During ITG treatment growth hormone levels were slightly increased. Although there was a trend to worsening on the CGI and PGI during ITG treatment, there were no significant differences between ITG and placebo treatment in any of the outcomes. ITG given over 4 weeks was ineffective for pain or dystonia in CRPS. Although no serious adverse events occurred, further studies are required to rule out potential neurotoxicity of ITG.
Introduction

Complex regional pain syndrome type 1 (CRPS), which is more common in women and often preceded by a trauma, is characterised by spontaneous pain, oedema, changes in skin temperature and colour, hyperhidrosis, and motor disturbances.\textsuperscript{1,2} The latter mainly include fixed dystonia of the distal extremities.\textsuperscript{3,4} The pathophysiology of CRPS is still unclear but over the last decade there is increasing evidence showing that different mechanisms may contribute to its broad clinical spectrum.\textsuperscript{1,5,6}

The initial symptoms of CRPS have been attributed to a perturbed regulation of inflammation in which both C and A\textdelta sensory nerve fibers (neurogenic inflammation) and the immune system of the skin are involved.\textsuperscript{7-10} Peripheral inflammation or injury may in turn lead to profound changes in the processing of sensory input at the spinal level, a process known as central sensitisation.\textsuperscript{11,12} As a result, pain may become chronic and allodynia and hyperalgesia may develop. Additionally, these central changes may corrupt the normal control of motor circuits.\textsuperscript{13,14}

Compelling evidence from neurophysiological studies that focused at the spinal or cortical level in patients show that disinhibition is a key characteristic in the involvement of the central nervous system in CRPS patients with and without dystonia.\textsuperscript{15-18} Cutaneous C and A\textdelta afferents are linked to spinal interneuronal circuits that mediate nociceptive withdrawal reflexes (NWRs).\textsuperscript{19} Interestingly, both sensitised NWRs in animal models and pain and dystonia in CRPS patients respond to the intrathecal administration of the GABA\textsubscript{B} agonist baclofen (ITB), which enhances spinal GABA-ergic inhibition.\textsuperscript{20-22}

In addition to GABA-ergic circuits, glycinergic circuits may also be involved in central sensitisation. In rats, peripheral inflammation-induced central sensitisation has been associated with loss of glycinergic inhibition.\textsuperscript{23} Following peripheral inflammation or spinal PGE\textsubscript{2} injection, mice with a glycine receptor deficiency showed a reduced pain sensitisation.\textsuperscript{24,25} In animal models of neuropathic pain, intrathecal glycine (ITG) reduced\textsuperscript{26,27} or prevented\textsuperscript{28} hyperalgesia. Besides involvement in afferent processing, glycine may play a prominent role in the control of motor functions. Strychnine is a glycine receptor antagonist, and poisoning with this drug results in overwhelming muscle spasms, rigidity and tremor.\textsuperscript{29} Glycine receptor mutations in both humans and animals result in spasms, tremor and myoclonia,\textsuperscript{30,31} motor features that bear a remarkable similarity to those reported in CRPS.

In view of the important role of disinhibition in chronic CRPS and the potential role of glycinergic mechanisms in pain and motor processing, drugs such as glycine that enhance
glycinergic inhibition may provide a new mode of treatment in CRPS. Because glycine is abundantly present in food, it would seem plausible that this potentially dangerous inhibitory neurotransmitter has limited access to the CNS. Indeed, two animal studies have reported a poor blood-brain barrier (BBB) passage of glycine. As a consequence, glycine requires intrathecal administration (ITG) to explore its role in the management of pain and dystonia in CRPS.

Aims of the current study were to evaluate the safety and efficacy of ITG in patients with CRPS. We here report the results of a double-blind randomised placebo-controlled crossover trial evaluating 4 weeks of ITG treatment in 20 chronic CRPS patients.

Methods

Subjects were male or female out-patients, at least 18 years of age, with a clinical diagnosis of CRPS with dystonia who were referred to the movement disorders outpatient clinic of the Department of Neurology and were candidates for ITB treatment. Patients who qualified for ITB treatment were requested to participate in the current study, which was performed in the period before ITB treatment started. Patients were referred by physicians throughout the Netherlands. Inclusion criteria were CRPS 1 according to the diagnostic criteria of the International Association for the Study of Pain, clinically significant fixed dystonia in one or more extremities, and symptoms for at least 1 year. Exclusion criteria were satisfactory relief of symptoms with conventional treatments including oral baclofen, pregnancy, breastfeeding, childbearing potential without using effective contraception, clinically significant psychiatric illness, suspicion of poor compliance, or involvement in legal proceedings concerning compensation for CRPS. All patients were evaluated by a psychiatrist to exclude psychiatric comorbidity. In all subjects a programmable SynchroMed pump (Medtronic, Minneapolis, MN) for continuous IT administration was implanted. The catheter was introduced in the subarachnoid space (L2-L3) under X-ray guidance with the distal tip of the catheter placed in the midthoracic region. The catheter was then tunneled subcutaneously and connected to the pump. Pump-catheter system integrity was verified post-operatively. We aimed to recruit 20 patients, which was considered a reasonable sample size for a first safety study. Patient consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethics Committee of the Leiden University Medical Centre.
N=1 experience
To date no published studies on ITG in humans are available. The dose schedule of ITG in
the current study was based on our experiences in one CRPS patient who progressed to
generalised dystonia and did not respond to ITB. After consent was obtained from both
the local Ethics Committee and the patient, a last resort therapy with ITG was started. We
noted a sustained and prominent decrease in pain with moderate effects on dystonia at a
dose of 30 mg/24 h. ITG was administered for 1 year and no side-effects occurred.

Study design
We used a double-blind randomised placebo-controlled crossover design. Randomization
was done by a computer-generated list and took place at the Department of Pharmacy.
Treatment allocation remained concealed from patients and investigators (including those
who performed the assessments) throughout the study. Every subject received two
intrathecal treatments: 21 mg/mL glycine solution during 4 weeks, and sodium chloride
0.9% (w/v) during 4 weeks (placebo), with a tapering and wash-out period in-between
both treatments: tapering in 1 week (3 equal dose reductions with an interval of 48 h),
followed by a wash-out period of 1 week. The carry-over between treatments was considered
minimal because the plasma half-life of IV glycine ranges from 30-60 min\(^{35}\) (the half-life of ITG
is unknown). Placebo and ITG have the same watery appearance, which made unblinding by
inspection of the administered substances impossible. Treatment was started at 8 mg/24 h
and was increased weekly with 8 mg/24 h. Unless side-effects occurred, glycine
administration reached a daily dose of 32 mg/24 h in the last week of the glycine period.
Higher dose administrations were not studied because of the associated short filling interval
(<1 month) of the pump, which was considered not feasible in clinical practice.

An independent data safety board monitored the study. The committee monitored the
safety of the patients by evaluating the treatment-emergent adverse events (AEs). The
study is registered with the Netherlands Trial Register, number NTR499.

Outcome measures
Safety assessments included history taking, physical examination and routine blood
assessments (every other week) and electrocardiograms (every other week). Pain was
evaluated with a numeric rating scale (NRS) for pain, and the McGill pain questionnaire.\(^{36}\)
A TSA-II thermal sensory analyzer (Medoc Ltd., Ramat Yishai, Israel), using a thermode
placed on both hands (thenar eminences), was used to assess detection thresholds of
temperature change (method of limits). Efficacy on movement disorders was studied with the Burke-Fahn-Marsden (BFM) dystonia rating scale, unified myoclonus rating scale (sections 2, 3, and 4) and tremor research group rating scale (items 1-8). Assessment of activity level included the Radboud skills questionnaire (if arms were involved) and the walking ability questionnaire (if legs were involved). Change of CRPS signs and symptoms was rated on a global impression scale: both the investigator (clinical global impression, CGI) and the patient (patient's global impression, PGI) assessed the change during treatment on a scale ranging from -3 (very poorly) to +3 (very well). Success of the blinding was investigated by asking both the patient and investigator to guess which treatment was administered.

Plasma glycine and growth hormone analysis
Blood samples for glycine measurement were taken at the last day of treatment (before tapering). Blood was collected in EDTA (ethylene diamine tetraacetic acid) tubes and directly cooled with melting ice. Plasma was isolated after centrifugation at 20°C for 7 min at 1,500g and stored at -20°C until analysis. Glycine was determined on a Biochrom 30 automated amino acid analyzer (Biochrom, Cambridge, UK) as previously described; however 250 µM L-methionine sulfone (Sigma, St Louis, MO) was used as the internal standard and a short buffer program of 50 min was used.

Because in a previous study in children, IV glycine increased growth hormone (GH) levels, blood levels of GH were monitored at baseline and at the last day of each of the interventions.

Statistical analysis
To study differences between 4 weeks of ITG treatment and 4 weeks of placebo treatment, the paired t-test (if data were normally distributed) or Wilcoxon test (if not) were used. Significance was assumed at the 0.05 level. For all tests, the SPSS software package version 14.0 (SPSS Inc., Chicago, IL) was used.

Results
No patients refused to participate in the study in the period before their ITB treatment started. Patients were aged 26-58 years (19 women, 1 man). One patient withdrew her consent after implantation. The remaining 19 patients entered the study (Table 8.1).
one patient, the study was ended prematurely because participation was experienced as too burdensome (she received ITG during 21 days, and no placebo).

Table 8.1. Baseline characteristics - before pump implantation (n=19)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>18/1</td>
</tr>
<tr>
<td>Age (yr; median, IQR)</td>
<td>41 (34-51)</td>
</tr>
<tr>
<td>Duration of CRPS (yr; median, IQR)</td>
<td>9 (5-17)</td>
</tr>
<tr>
<td>Number of dystonic extremities (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6 (31)</td>
</tr>
<tr>
<td>3</td>
<td>3 (16)</td>
</tr>
<tr>
<td>4</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Modified Rankin scale (%)</td>
<td></td>
</tr>
<tr>
<td>No significant disability</td>
<td>0</td>
</tr>
<tr>
<td>Slight disability</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Moderately severe disability</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>0</td>
</tr>
</tbody>
</table>

CRPS = complex regional pain syndrome type 1; IQR = interquartile range.

Safety
Treatment-emergent AEs were found in 15 patients. The most frequently reported AEs were drowsiness, headache, dysesthesia and nausea and vomiting (Table 8.2). The proportion of patients with one or more AEs was similar during ITG (12/19 = 63%; 18 AEs) and placebo treatment (9/18 = 50%; 13 AEs; \( \chi^2 = 0.23, \text{df} = 1, \ p = 0.63 \)). Serious AEs did not occur. Other AEs during ITG treatment were categorized as mild to moderate. In one patient, a mild but persistent exacerbation of pain and dystonia occurred, which began at the first day of ITG treatment.

Plasma glycine and GH measurements
Mean plasma glycine concentrations were not different between ITG treatment (242 μM, range 106-461) and placebo treatment (241 μM, range 105-499) at 28 days of treatment (\( p = 0.75 \), paired t-test).
Table 8.2. Treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>ITG (n=19)</th>
<th>Placebo (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dyseusia</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Photopsia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Restless legs</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Emotional liability</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Polyuria</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Unpleasant feelings</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Fever (1 day)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CRPS exacerbation</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>19</strong></td>
<td><strong>14</strong></td>
</tr>
</tbody>
</table>

CRPS = complex regional pain syndrome type 1; ITG = intrathecal glycine.

At baseline, four patients had GH values (8.8, 9.8, 25.9 and 70.6 mU/L) above the normal range (0.0-5.0 mU/L). GH was significantly increased at day 29 of ITG treatment (median 2.1, interquartile range [IQR] 0.7-5.3, maximum 30.7 mU/L) compared to day 29 of placebo (median 0.9, IQR 0.5-4.2, maximum 13.4 mU/L; $P=0.031$, Wilcoxon test). There were no significant abnormalities in other clinical laboratory tests or electrocardiograms.

**Efficacy**

There were no significant differences in any of the outcome measures, between ITG and placebo treatment (table 8.3). During ITG treatment, one patient reported improvement (PGI +2), and nine reported worsening (PGI -3 in one patient, -2 in four, and -1 in four). The CGI score showed improvement in one patient during ITG treatment (+2), and worsening in five (-3 in one, and -1 in four). During placebo treatment, two patients reported improvement (PGI +2), and four reported worsening (-2 in three, and -1 in one), the CGI showed improvement in none, and worsening in one (-1). The effect of placebo was 0% for the pain NRS and -15% for the BFM dystonia rating scale.

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Table 8.3. Summary of secondary outcome events (medians (interquartile ranges) are presented)

<table>
<thead>
<tr>
<th>Outcome event</th>
<th>Range scale</th>
<th>Intrathecal glycine</th>
<th>Placebo</th>
<th>P^b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>4 weeks</td>
<td>Baseline</td>
</tr>
<tr>
<td>Pain (numeric rating scale)</td>
<td>0-10</td>
<td>6 (4-8)</td>
<td>6 (5-8)</td>
<td>7 (5-8)</td>
</tr>
<tr>
<td>McGill pain questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of words chosen</td>
<td>0-20</td>
<td>12 (7-13)</td>
<td>13 (8-14)</td>
<td>12 (8-14)</td>
</tr>
<tr>
<td>Pain rating index</td>
<td>0-63</td>
<td>21 (11-28)</td>
<td>20 (13-32)</td>
<td>22 (14-28)</td>
</tr>
<tr>
<td>Thermal sensory analyzer (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold detection threshold (∆T)</td>
<td>0.1-17.0</td>
<td>1.3 (0.3-4.7)</td>
<td>1.0 (0.3-3.8)</td>
<td>1.0 (0.4-5.6)</td>
</tr>
<tr>
<td>Heat detection threshold (∆T)</td>
<td>0.1-18.5</td>
<td>1.4 (0.5-5.1)</td>
<td>1.8 (0.9-4.3)</td>
<td>2.3 (1.2-6.1)</td>
</tr>
<tr>
<td>Burke-Fahn-Marsden dystonia rating scale</td>
<td>0-120</td>
<td>32 (14-44)</td>
<td>35 (12-48)</td>
<td>27 (12-41)</td>
</tr>
<tr>
<td>Unified myoclonus rating scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonus at rest</td>
<td>0-128</td>
<td>0 (0-8)</td>
<td>0 (0-5)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Stimulus sensitivity</td>
<td>0-17</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Myoclonus with action</td>
<td>0-160</td>
<td>10 (0-20)</td>
<td>0 (0-16)</td>
<td>3 (0-20)</td>
</tr>
<tr>
<td>Tremor research group rating scale (items 1-8)</td>
<td>0-76</td>
<td>2 (0-6)</td>
<td>2 (0-6)</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>Radboud skills questionnaire (total)</td>
<td>1-5</td>
<td>4 (3-5)</td>
<td>4 (3-4)</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Walking stairs questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking in the house</td>
<td>0-10</td>
<td>9 (8-10)</td>
<td>9 (6-10)</td>
<td>9 (6-10)</td>
</tr>
<tr>
<td>Walking outside</td>
<td>0-10</td>
<td>10 (7-10)</td>
<td>10 (7-10)</td>
<td>10 (9-10)</td>
</tr>
<tr>
<td>Patient’s global impression</td>
<td>-3±3</td>
<td>0 (-1-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Clinical global impression</td>
<td>-3±3</td>
<td>0 (-2-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
</tbody>
</table>

^aBest score is underlined.

^bITG at 4 weeks versus placebo at 4 weeks (Wilcoxon signed rank test).

Patient's and investigator's guesses of which treatment was administered were incorrect in 57% and 59%, respectively. There was no significant effect of sequence (ITG-placebo or placebo-ITG) on the pain NRS and BFM dystonia rating scale baseline scores.
Discussion

Central disinhibition plays an important role in CRPS and enhancing the GABA-ergic inhibitory status through intrathecal administration of baclofen has proven beneficial in the treatment of dystonia and to a lesser extent on pain.\(^{21,22,46}\) Against this background, we were interested if similar results could be obtained by enhancing glycinergic inhibition in CRPS patients. Because no information is available on the tolerability of this mode of glycine administration in humans, this study firstly focussed on the safety of ITG and secondly evaluated its efficacy in doses up to 32 mg/24 h. No major AEs occurred in 19 CRPS patients treated with ITG over 4 weeks. The proportion of most frequently reported AEs (drowsiness, headache, dysesthesia and nausea and vomiting) was similar for ITG and placebo treatment. Compared to placebo, median GH values increased during ITG treatment (0.9 versus 2.1 mU/L). GH levels still remained in the normal range of 0-5.0 mU/L, and were smaller than the increases that are observed with intravenous GH. Notably, the absence of functional disturbances in our patients is at best only a surrogate marker for the absence of neurotoxicity of ITG.\(^{47}\) Evolving deficits may not be revealed by functional indices for an extended period of time, whereas histological examination demonstrates a continuing event.\(^{48}\) Consequently, our findings are insufficient to assume that ITG is not associated with neurotoxicity and further studies are required to address this issue.

Over the dose-escalation period of 4 weeks with doses up to 32 mg/24 h we did not find evidence of efficacy of ITG. Several explanations for this lack of efficacy of ITG are possible. First, it is possible that not glycinergic but GABA-ergic mechanisms play a key role in central disinhibition of CRPS. Second, ITG may have been administered in an insufficient dose, although GH-increases indicate that the doses were pharmacologically active. Third, effective synaptic concentrations of glycine are regulated by glycine transporters which mediate its uptake into nerve terminals and adjacent glial cells.\(^{49}\) Hence, the lack of efficacy of ITG could result from a compensatory ITG-mediated increased activity of glycine reuptake transporter mechanisms. In this case, selective inhibitors of glycine transporter could be more efficacious. Finally, however, our patient and clinician-based impression scores may hint at another explanation. Although the primary outcomes showed no difference, there was a trend on the patient and clinician-based impression scores to show deterioration during ITG. Nine patients worsened during ITG, versus four during placebo treatment according to the patient-based PGI score. In line with this, the
investigator-based CGI indicated that five patients got worse during ITG, versus one patient during placebo treatment. Although, the PGI and CGI were not significantly different from zero, the trend towards a deterioration of signs and symptoms with ITG suggests that glycine may play a pathophysiological rather than a therapeutic role in CRPS. This could be caused by the dual action of glycine, which serves both as an obligatory co-activator of the spinal excitatory N-methyl-D-aspartate (NMDA) receptor, and as a neurotransmitter at the inhibitory strychnine-sensitive glycine receptor.\textsuperscript{50,51} It is possible that the excitatory effects prevailed in the applied dose range. In CRPS, chronic pain, allodynia, and hyperalgesia, are assumed to result from central sensitisation, a state reflecting enhanced synaptic transmission efficiency of neurons in the dorsal horn of the spinal cord.\textsuperscript{11} In central sensitisation, the NMDA receptor is upregulated, and open studies using NMDA antagonists memantine and ketamine have reported beneficial effects on pain in CRPS.\textsuperscript{52-54} Hence, ITGs efficacy could depend on the state of the NMDA receptor and stimulation of the excitatory glycine receptor of the upregulated NMDA receptor may potentially worsen symptoms such as pain, explaining the trend of poorer ratings of patients and physicians when patients were using ITG.\textsuperscript{55-57} Interestingly, intrathecal administration of 2-amino-5-phosphonopentanoate, an NMDA receptor antagonist, unmasked the analgesic action of glycine in rats.\textsuperscript{58} Hence, future studies could analyze whether or not NMDA inhibition, administered prior to or simultaneously with ITG may enhance its therapeutic potential under circumstances of central sensitisation. Because intrathecal administration of NMDA inhibitors is neurotoxic,\textsuperscript{59} this hypothesis can only be tested with orally or intravenously administered agents.

We studied a population of severely affected CRPS patients with long disease duration. Consequently, this patient sample involved a selection of treatment refractory patients, who are not representative for all CRPS patients. However, it would be unethical to evaluate ITG in acute stage patients, in whom symptoms might resolve spontaneously or following less invasive treatment options.

There is no data on the magnitude of the placebo responses in trials evaluating chronic treatment in CRPS patients with dystonia until now. In our previous study, placebo responses to two intrathecal saline injections were 4% and 8%, respectively.\textsuperscript{21} Interestingly, there was no detectable placebo response in the current study during 4 weeks of intrathecal treatment. This finding might be useful for designing future trials on this subject.
In conclusion, ITG in doses up to 32 mg/24 h during four weeks was not associated with serious adverse events, but further studies are required to rule out potential neurotoxicity of ITG. Although results from animal studies were promising, this study did not find efficacy on pain or dystonia in patients with chronic CRPS. Several potential explanations for this finding could be addressed in future studies.

Acknowledgements: We thank A.S. Salm for her support in patient care.

Appendix
The data safety board consisted of Prof.dr. H.J. Guchelaar (Department of Clinical Pharmacy, Leiden University Medical Centre), Dr. R.J.E. Grouls (Department of Clinical Pharmacy, Catharina Hospital, Eindhoven) and Dr. G.J. Lammers (Department of Neurology, Leiden University Medical Centre).
References

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