Abstract

Introduction: Memantine was discovered in 1968 and is used as a treatment for Alzheimer’s disease. We evaluated the use of memantine to treat complex regional pain syndrome in this retrospective study.

Patients and methods: 56 patients with CRPs, who were treated with trial of memantine for at least two months with 40mg QHS from 2007 until 2009.

Results: 34 females and 22 male patients. Age-46.0±/-9.7 years. Number of years with CRPS-9.24 ± 5.7 years. Memantine was started at 5 or 10mg QHS, before being increased by 5 or 10mg every 4-7 days, as tolerated, to a maximum dose of 40mg-60mg, as tolerated. In all, 13 patients showed complete remission from CRPS with VAS 0 and the disappearance of allodynea for at least nine months after the use of memantine. In addition, 18 patients showed partial improvement of VAS and allodynea. Eight patients showed no improvement even after continuous use of memantine at a dose of 40mg QHS for two months. Seven patients could not take more than 5mg of memantine per day and had to stop it due to side effects. In terms of subjective improvement in short-term memory, nine patients showed much improvement, 14 patients showed some improvement, three patients showed no changes and one patient did not answer the questionnaire. Regarding subjective feelings of having a better quality of life, 17 patients answered yes, three did not feel any changes, six could not give an answer and two did not fill out the questionnaire.

Conclusions: Memantine is a promising option for the treatment of CRPS. A randomised controlled study is needed to evaluate its efficacy.

Introduction

Bowsher (1991) found that neuropathic pain affected 25-50% of chronic pain patients in most pain clinics. Richards (1967) reported the history of CRPS and its terminology. Although previous descriptions were of single cases, Weir Mitchell, Morehouse and Keen (1864) first described the condition in full in the book “Gunshot Wounds and other Injuries of Nerves”. The
authors described the condition as a burning pain, which Weir Mitchell later described as causalgia in 1872 in the Merck Manual for Health Professionals. Thomas and Grossberg explained the multimodal therapies and treatments used for Alzheimer’s disease, including memantine which was discovered 1968.

Sines et al. (2007) published his preliminary report on the use of memantine in complex regional pain syndrome with promising results. Schley et al.’s (2007) experiment with memantine in patients with phantom limb pain, in combination with continuous brachial plexus blocks, showed a decrease in phantom pain up for to six months. However, treating CRPS remains an off-label use for memantine. In this study, we evaluated the use of memantine in patients with complex regional pain syndrome.

Patients and methods

We reviewed the charts of patients with diagnosed with CRPS that were treated in our clinic from 2007 until 2009. In all, 56 CRPS patients (52 CRPS I, four CRPS II) were treated with memantine, including 34 females and 22 males. Retrospective, open label data and results were gathered from treating our patients during at least two years of follow-up after beginning memantine. All patients consented to the off label use of memantine for the treatment of CRPS.

Table 1
Patient Demographics

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>42.9</td>
<td>21</td>
<td>Male</td>
</tr>
<tr>
<td>57.1</td>
<td>28</td>
<td>Female</td>
</tr>
<tr>
<td>100.0</td>
<td>49</td>
<td>Total</td>
</tr>
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</table>

Patients received a minimum dose of 40mg/day-60mg/day, as long as a better response was achieved with no side effects. Seven patients were excluded from the study because they did not tolerate a memantine dose of even 5 mg a day. Five of the seven patients had already been diagnosed with bipolar affective disorder at least two years prior to their CRPS diagnosis and were on antipsychotic medications and mood stabilisers prior to receiving the memantine. Severe hallucinations, wild dreams, and psychotic ideations were the frequent complaints while on memantine.

The mean age of the participants was 46.0 ± 9.7 years. The average number of years since the participants’ diagnoses of CRPS was 9.24 ± 5.7 years. Memantine was started at 5 or 10mg QHS, before being increased by 5 or 10mg every 4-7 days, as tolerated, up to a maximum level of 40mg, or 60mg if a better response was achieved with no side effects. No changes were made in any of the patients’ current poly-pharmacy treatment plans for CRPS during the experiment until the patients asked for to stop or decrease their non-experimental medications.

Before the starting memantine, all of our patients had been taking a large variety of CRPS treatments including:

Several diagnostic/therapeutic sympathetic blocks (all patients), and/or continuous sympathetic blocks (if possible, some patients).

<table>
<thead>
<tr>
<th>Std. Error</th>
<th>Std. Deviation</th>
<th>N</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>.20065</td>
<td>1.40456</td>
<td>49</td>
<td>8.163</td>
</tr>
<tr>
<td>0.44134</td>
<td>3.08937</td>
<td>49</td>
<td>3.5510</td>
</tr>
<tr>
<td>.29776</td>
<td>2.08432</td>
<td>49</td>
<td>7.7755</td>
</tr>
<tr>
<td>.41853</td>
<td>2.92973</td>
<td>49</td>
<td>3.7143</td>
</tr>
</tbody>
</table>

A number of months of proper physical therapy.

Psychological therapy, if needed.

Extensive poly-pharmacy therapy: membrane stabilisers, NSAIDs, anti-depressants, muscle relaxants, alpha-2 agonists, alpha-1 antagonists, steroids, opioids and/or biphosphonats.

A few had intrathecal delivery systems ([opioids/baclofen/clonidine/local anaesthetic] combinations).

A few had epidural Dorsal Column Stimulation for pain modulation.

A few had a combination of treatments five and six.

Each patient was encouraged to maximise participation in daily living activities.
All patients received a monthly evaluation for signs of changes in:

- Allodynia
- Burning pain
- Short-term memory loss
- Anger level
- Normalcy in everyday life

To assess for burning pain, the following assessments were used:

1) Quantitative Visual Analog Scale (VAS) before and after six months on the full dose of memantine.
2) Quantifying the number of exaggerated burning attacks per month on the primary CRPS extremity (patients voted to call these “a 10/10 Fire Storm”).

Allodynia was assessed according to the following:

1) Percentage of decrease of the disgusting unpleasing feelings related to soft touch of the skin of the area affected by CRPS.
2) For the patients that enjoyed taking a shower prior to the development of CRPS, the time spent in the shower from before and after six months on memantine.

To assess for CRPS-related migraine headaches, a quantitative decrease in the number of migraine attacks/month before and after six months on memantine was examined.

We followed the patients for at least two years after the start of the memantine.

**Results**

In all, 56 patients were enrolled in the study, and ultimately, seven were excluded, as they did not tolerate the memantine. Of the patients that were excluded, six were females and one was male. Five of the seven patients had been already diagnosed with bipolar affective disorder at least two years prior to the CRPS diagnosis, and were on antipsychotic medications and mood stabilisers prior to beginning memantine. Severe hallucinations, wild dreams, and psychotic ideations were the frequent complaints related to side effects while on memantine. Out of the 49 patients that continued to use memantine, 21 were male (42.9%) and 27 were female (57.1%).

The mean VAS was 8.1633 (SD: 1.40456) before the use of memantine and 3.5510 (SD: 3.08937) after the use of memantine, which was statistically significant at $p < 0.001$. Those that responded positively to the memantine did not ask for any increase in other pain medications, and instead, asked for the dosages of the other medications to be decreased. The mean burning pain was 7.7755 (SD: 2.08432) before the use of memantine and 3.7143 (SD: 2.92973) after the use of memantine, which was statistically significant at $p < 0.000$. Out of 49 patients, 13 (26.5%) showed a complete disappearance of the pain, burning and allodynia.

**Discussion**

Memantine is a drug with the ability to block NMDA receptors in the brain. Juliato Piovesan et al. (2008) suggested that memantine was much more potent inhibitor of central and peripheral sensitisation than were non-NMDA antagonists. Park et al. (2012) tested the drug on trigeminal pain in rats. Belozertseva and Bespalov (1998), as well as Popik and Kozela (1999), showed that memantine could attenuate the tolerance to morphine in animal models. Davidson and Carlton’s (1998) experiment demonstrated that the local use of memantine in attenuating pain in animal models was comparable to the use of dexmethylorphan and ketamine. Eisenberg et al. (1998) failed to find clinical benefits of using memantine for post-herpetic neuralgia when using doses of 10-20mg/day. Nikolajsen et al. (2000), in a randomised cross-over study, could not find any difference when using 20mg/day of memantine after amputation or nerve injury surgery. Siniset al. (2007) published preliminary results in human patients with CRPS that had good responses to the medication when using 20 mg/day. Scheley et al. (2007) found a decrease in the medication requirements, as well as in the phantom limb pain, when using memantine at doses of 20-30mg/day compared to those people that did not use the drug. Grande et al. reported the use of memantine with small doses of ketamine for opioid tolerant oncology patients, demonstrating less opioid consumption at memantine doses of 20mg a day, and recommended more studies be done in this area. Thomas and Grossberg (2009)
recommended the use of memantine for Alzheimer’s disease and other neuropsychiatric diseases due to its level of safety. Olivan-Blázquez et al. (2014) found promising results for memantine use at doses of 20g/day when used for fibromyalgia.

We used the memantine in our practice for resistant cases of CRPS and used larger doses than what was recommended for use in patients with Alzheimer’s disease (40mg/day), which could be why other studies results did not show the same benefits. Also, in our study, the pathology was different than in the other studies, which might also contribute to the conflicting results. Our study was limited in the lack of randomisation with a controlled group that used a placebo. However, in our study, we compared the same patient before and after the use of memantine, using the patients’ data before the treatment as the control. We concluded that memantine is effective and is a promising option for the treatment of CRPS. More studies are needed using blinding, randomisation and possibly placebo procedures.

References

The key to

Lock-up

Postoperative Pain

**Initial bolus**
Inject 1 ampoule Tramal® 100 mg i.v. or i.m. slowly over 2-3 minutes

**Ways of administration after initial bolus**

- **Infusion**
  - Inject 2 ampoules Tramal®, each 100 mg, in 500 ml of infusion solution.
  - Infusion rate 12-24 mg Tramal®/h (160-200 ul/minute or 30-60 ul/min).
  - Subsequent increments of 30 mg with a wash-out time of 5 minutes.
  - usual dose is 50 mg or 100 mg 4-hourly up to a total daily dose of 400 mg except in special clinical situations which might necessitate daily dose up to 480 mg.
  - Further treatment with Tramal® should be on demand.

- **PCA**
  - Usual dose is 50 mg or 100 mg 4-hourly up to a total daily dose of 400 mg (excluding the initial bolus) within the first 24 hours.

- **Injection**
  - Inject 1-2 capsules every 4-6 hours
  - 20-40 drops every 4-6 hours
  - 1 suppository every 4-6 hours

**Follow-up**
- 50 mg slow release 100 mg, 150 mg, 200 mg 1 tablet every 12 hours

**Intra-Operative**

- **Loading Dose**
  - 2.5 - 3 mg/kg at wound closure

**Post-Anaesthesia Care Unit**

- **Loading Dose**
  - If intra-operative dose not given then bolus i.v.
  - 100 mg over 2-3 mins

An intra-operative loading dose of Tramal® will reduce PONV rates

References:

For patients with localized BURNING SHOOTING STABBING Neuropathic pain WORKS WHERE IT HURTS
BRIDION—**for optimal neuromuscular blockade management and improved recovery**

**Predictable and complete reversal**

- 98% of BRIDION patients recovered to a TOF ratio of 0.9 from reappearance of T2 within 5 minutes.
- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs within 5 minutes.

**Rapid reversal**

- BRIDION rapidly reversed patients from reappearance of T2 in 1.4 minutes.
- BRIDION rapidly reversed patients from 1 to 2 PTCs in 2.7 minutes.

**BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.**

**Important safety information**

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

**BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the Intensive Care Unit (ICU) setting.** If neuromuscular blockade is required within 24 hours of BRIDION administration, a non-steroidal neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or sucking on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (e.g., flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (17%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exerted in patients on anticoagulation for a pre-existing or comorbid condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fucidic acid, and hormonal contraceptives.

**References:**
1. BRIDION Summary of Product Characteristics (SPC).

**Please see summary of product characteristics for full prescribing information.**
Pioneering Medical Technology

TAP Block And InfiltraLong
For Effective Treatment
Of Long And Deep Incisions

Sono Cannulas
For Single Shot UltraSound
Guided Nerve Blocks

SonoSystem And SonoLong Curl
For UltraSound Guided Nerve Blocks

Sprotte® 2.G
The New Generation
Dura Puncture In Minimum Time

SonoEye Ophthalmic Block
For Peribulbar And Retrobulbar
Blocks Under Ultrasonic Monitoring

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