Review article

The analgesic effect of intravenous lidocaine in the treatment of chronic pain: a literature review

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ABSTRACT

Background: Pain is a public health problem, greatly impairing quality of life. Almost 80% of patients with chronic pain reported that their pain interferes with activities of daily living, and two thirds reported that the pain causes negative impact on their personal relationships. The physical and functional disability, whether temporary or permanent, compromises the professional activity and causes work absenteeism, increasing costs of health systems.

Objectives: The aim of this review is to analyze, based on the literature, the analgesic effect of lidocaine administered intravenously for the treatment of chronic pain and to evaluate the reduction of pain intensity in patients with chronic pain, focusing on musculoskeletal and neuropathic etiology.

Methodology: The method used was a review of the literature, consisting in searching the scientific literature on the efficacy of intravenous lidocaine infusion in the treatment of patients with chronic pain.

Content: Of the 19 studies reviewed, 12 had results that confirm the analgesic effect of intravenous lidocaine in patients with chronic pain. Most authors used doses of 5 mg/kg infused for 30 minutes or more, producing significant analgesia with variable duration (minutes to weeks).

Conclusions: Based on the literature review, it is not possible to uniformly specify the most effective and safe dose of lidocaine administered intravenously for the treatment of neuropathic or musculoskeletal pain. As for effectiveness, the intravenous infusion of lidocaine as an alternative for the treatment of chronic pain of various etiologies seems very promising, but further studies need to be conducted.

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2255-5021 © 2014 Elsevier Editora Ltda. All rights reserved.
A ação analgésica da lidocaína intravenosa no tratamento da dor crônica: uma revisão de literatura

RESUMO

Justificativa: A dor é um problema de saúde pública, comprometendo sobremaneira a qualidade de vida. Quase 80% dos pacientes com dor crônica relataram que a dor interfere em suas atividades da vida diária, e dois terços afirmaram que a dor provoca impacto negativo nas relações pessoais. A incapacidade física e funcional, seja temporária ou permanente, compromete a atividade profissional e causa absentismo ao trabalho, elevando os custos dos sistemas de saúde.

Objetivos: O objetivo desta revisão é analisar, com base na literatura, o efeito analgésico da lidocaína administrada por via intravenosa no tratamento da dor crônica e avaliar a redução da intensidade da dor em pacientes com dor crônica, focando a etiologia musculoesquelética e neuropática.

Metodologia: O método adotado foi o de revisão da literatura, consistindo na busca de artigos científicos sobre a eficácia da infusão intravenosa de lidocaína no tratamento de pacientes com dor crônica.

Conteúdo: Dos 19 estudos revisados, 12 apresentaram resultados que confirmam a ação analgésica da lidocaína por via intravenosa em pacientes com dor crônica. A maioria dos autores utilizou doses de 5 mg/kg infundidas por 30 minutos ou mais, produzindo analgesia significativa com duração variável (de minutos a semanas).

Conclusões: Com base na revisão da literatura, não é possível uniformemente especificar a dose mais eficaz e segura de lidocaína administrada por via intravenosa no tratamento da dor neuropática ou musculoesquelética. Quanto à eficácia, a infusão intravenosa da lidocaína como alternativa para o tratamento da dor crônica de etiologias diversas parece bastante promissora, embora estudos adicionais necessitem ser realizados.

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Introduction

Chronic pain affects approximately 7% to 40% of the world population. In Brazil, a study conducted by WHO, in 1998, showed a prevalence of 31% (data from Rio de Janeiro); on the other hand, in Salvador, Bahia, it is estimated that 41.4% of the population suffers from chronic pain.1

Pain is a public health problem, greatly impairing the quality of life. Several factors, such as depression, sleep disturbances, difficulty concentrating, hopelessness, feelings of death and others, are associated with this symptom. The loss of quality of life is a fact, as the pain begins to guide and limit the behavior and activities of the subject, generating social withdrawal, changes in sexuality, changes in family dynamics and economic imbalance. Nearly 80% of patients with chronic pain reported that their pain interferes in activities of daily living, and two thirds said that the pain causes negative impact on personal relationships. Physical and functional disability, whether temporary or permanent, jeopardizes the professional activity6 and causes work absenteeism, increasing the costs of health systems. In the United States, for example, it is estimated that over 50 million working days are lost each year. Thus, chronic pain is an important medical and social problem, and opioid abuse is of great concern, due for the problems stemming from their multiple side effects, including addiction.

Often the complexity of the pathophysiological mechanisms that explain the initiation and maintenance of pain makes difficult the assessment, diagnosis and treatment of pain syndromes that may present inflammatory, neuropathic or mixed components. Thus, there are several classes of drugs used in the treatment of chronic pain patients, in an attempt to reduce the intensity of pain and improve their quality of life. Among the local anesthetics, lidocaine [2-(diethylamino)-N-(2,6 dimethylphenyl) acetamide], a weak base with antiarrhythmic properties, has been used by various routes, including intravenous.

Lidocaine alters the transmembrane conductance of cations, especially sodium, potassium and calcium, both in neurons and myocytes. Voltage-dependent sodium channels constitute its classical targets, and the affinity of the drug for the channel is greater when it is opened (activated or inactive). Thus, the degree of blocking varies according to the neuronal stimulation frequency. However, other mechanisms are also involved in the analgesia provided by lidocaine as, for instance, the interaction, whether direct or indirect, with different receptors and pathways of nociceptive transmission, like the muscarinic agonists, glicine inhibitors, release of endogenous opioids and of adenosine triphosphate, and the reduced production of excitatory amino acids, neuropeptides and thromboxane A2.

Although lidocaine is typically administered through local injections, it is also used intravenously for various purposes, such as regional anesthesia, as an anti-dysrhythmic agent, in the relief of peripheral and central neuropathic pain, fibromyalgia treatment, and as an adjuvant in postoperative pain.
For these reasons, lidocaine is used in the treatment of patients with fibromyalgia, arthrosis, cancer, postherpetic neuralgia, neuropathic pain, and of patients with several other disorders causing chronic pain. Although control of chronic pain is difficult, many efforts have been directed towards the development of increasingly effective treatments, especially pharmacological ones, in reducing the intensity of pain in these patients and in providing longer periods of analgesia.

The aim of this review is to analyze, based on the literature, the analgesic effect of lidocaine administered intravenously for the treatment of chronic pain. The method adopted was to review the literature, consisting in the search for scientific articles, in this case, on the efficacy of intravenous lidocaine infusion in the treatment of patients with chronic pain. To this end, bibliographic databases, such as CENTRAL, MEDLINE/PubMed, LILACS and SciELO were searched. In the searching strategy, we used the following keywords
“lidocaine”, “intravenous and chronic pain”, or also “lidocaine, infusion and chronic pain”. Another strategy was a manual search in reference lists of those identified and selected articles by electronic search. We used as criteria for selecting the studies: publications until December 2012, with designs of the randomized clinical trial on humans type, which have been published in Portuguese or English, excluding other languages. Articles of relevance to lidocaine, as well as on disorders that present with chronic pain, were also included. Studies which evaluated the efficacy of lidocaine in relieving only evoked pain in animals, or that evaluated the efficacy of lidocaine with another drug, were discarded (exclusion criteria).

Intravenous lidocaine in the treatment of chronic pain conditions

Fibromyalgia

Several studies suggest that intravenous lidocaine can reduce the pain associated with fibromyalgia, although this is a condition refractory to other analgesic drugs. In a double-blind placebo-controlled trial conducted in the 90s, there was a decrease in pain scores during and after infusion of lidocaine.15 This finding is confirmed by subsequent studies, in that the duration of relief exceeded both the infusion time as the half-life of the drug.15 In an uncontrolled trial, five consecutive infusions of intravenous lidocaine with increasing doses of 2 mg/kg to 5 mg/kg resulted in a reduction in pain scores that was significant after the fifth day and persisted after 30 days.15 In another study, the reduction in pain scores was also maintained even 30 days after the last infusion of lidocaine.15 In a double-blind crossover trial involving 75 patients with fibromyalgia, a lasting analgesic effect of the drug was confirmed.15 On the other hand, other studies did not achieve positive results after the intravenous lidocaine infusion: after four infusions of the drug at weekly intervals, the observed reduction in pain scores was not statistically significant.16 In another study, which combined 3 mg/kg of intravenous lidocaine administered weekly with 25 mg of amitriptyline for 4 weeks, there was no change in pain intensity in patients with fibromyalgia, when compared with amitriptyline monotherapy.17

Myofascial pain syndromes

Most studies on intravenous lidocaine were performed in patients with neuropathic pain, while myofascial pain carriers are generally tested with an intramuscular infusion of the drug. In a study carried out in 2005, which involved infusions of lidocaine, ketamine and morphine, among 30 patients with chronic pain associated with whiplash lesion (cervical deceleration injury), 11 of 18 responders experienced pain reduction after lidocaine infusion at a dose of 5 mg/kg.18

Neuropathic pain

Peripheral neuropathies

Wallace et al. achieved significant analgesia in plasma concentrations of lidocaine between 1.5-2.5 mg/mL. In another study, a reduction in VAS score for continuous pain occurred when lidocaine was infused at high (5 mg/kg) and low (1 mg/kg) doses for periods of two hours or more. However, there were no differences in comparison with placebo.19

In the trial by Ferrante et al., the infusion of intravenous lidocaine demanded about five minutes to achieve maximal analgesia, and the analgesia increased abruptly from a certain plasma concentration (0.62 µg/mL).20 In other studies, the effect began 30 minutes after starting the infusion, reaching the peak effect within 60 to 120 minutes.21,22 In addition, there was significant analgesia compared to placebo for more than 6 hours after infusion, and a subset of patients reported relief for a still longer period, greater than 7 days.21

Reduction in pain intensity was also reported in patients with postherpetic neuralgia. The drug infusion at doses of 5 mg/kg or even 1 mg/kg for varying periods caused a significant reduction in pain scores,6 without, however, establishing a correlation between relief and plasma concentrations of the drug.

In patients with painful diabetic neuropathy, the duration of the individual effect varied between 3 and 28 days at doses of 5 or 7.5 mg/kg infused over a period up to 4 hours.23,24 with a trend to a greater response to lidocaine 7.5 mg/kg compared to 5 mg/kg, but this difference did not reach significance. The qualitative nature of pain was significantly modified by the drug, compared with placebo.24

Although several studies confirm the efficacy of lidocaine on continuous spontaneous pain caused by peripheral nerve injury, other experiments have failed to accordingly reaffirm the beneficial effect of the drug. A trial conducted in 2006, for example, demonstrated a significant reduction in pain evoked by repetitive stimuli, but not in spontaneous pain, after the infusion of 5.0 mg/kg for 30 minutes.25 The same negative result was observed by Gormsen et al.26 In a study comparing the effect of lidocaine with ketamine and placebo, lidocaine 2.5 mg/kg was not enough to generate significant differences versus placebo or ketamine. However, after the end of the infusion, patients who responded to lidocaine experienced a period of greater pain relief than patients who responded to ketamine, whose VAS scores virtually returned to pre-drug values after the end of infusion.27 Another experiment that used
increasing doses of the drug (1, 3 and 5 mg/kg) also failed to show analgesic effect of lidocaine at low doses, proving its effectiveness only at the highest concentration.\textsuperscript{26}

Lidocaine doses between 1.5 and 5.0 mg/kg proved effective to suppress ectopic discharge without blocking nerve conduction, corresponding to plasma levels of 0.62 to 5.0 mg/mL. Furthermore, the effect of systemic lidocaine on neuropathic pain may be different, depending on the source causing the pain. Thus, its effectiveness may be greater in patients with peripheral nerve injury than in those with pain due to damage to the central nervous system or of unknown etiology.\textsuperscript{29}

In cases of complex regional pain syndrome (CRPS), the use of intravenous lidocaine was reported to be beneficial in some patients when studied retrospectively, both in adults and in children.\textsuperscript{30,31} Controlled studies, however, failed to confirm these data. In an experiment that used a computer-controlled infusion pump, there was a significant decrease in the scores for spontaneous pain only when plasma lidocaine reached the highest level (3 mg/mL); plasma levels of 1 and 2 mg/mL did not cause a significant effect on spontaneous pain, which can be explained by the fact that this study involved intense neurosensory testing, that may have masked the effect of the drug.\textsuperscript{22}

Central pain

Systemically, lidocaine can induce significant and selective reduction of various components of pain caused by lesions of the central nervous system, including spontaneous pain, and two of 16 patients had relief for over 45 minutes after an infusion of 5 mg/kg of the active drug, compared with placebo.\textsuperscript{33} In another randomized, placebo-controlled trial, the drug alleviated neuropathic pain either below or at the level of the spinal lesion.\textsuperscript{34} These results are opposite to those found in a study carried out in 2004 in which only ketamine, and not lidocaine, was shown to reduce spontaneous continuous pain in patients with pain secondary to injury to the central nervous system.\textsuperscript{6}

The three aforementioned placebo-controlled studies evaluated the efficacy of intravenous lidocaine in central neuropathic pain. Two of them, using high doses of the drug (5 mg/kg IV) and including a total of 32 patients with traumatic spinal injury or syringomyelia, tested positive for spontaneous pain (both at the level of the spinal injury and below it), while the study using a smaller dose (1.5 mg/kg IV) had a negative outcome.

The analysis of Table 1 demonstrates the lack of uniformity of the studies in relation to the data presented: of the 18 articles analyzed, not all reported the dose of lidocaine or the infusion time; just some of them made some measurements of plasma concentration of the drug during infusion, and of those did it, few reported the minimal plasma level in which there was effect. Although the occurrence of adverse effects have been reported in most studies, some of them did not specify which reactions were observed. The vast majority of studies was limited to search the analgesic effect of lidocaine shortly after the infusion or, at most, a few hours later, refraining from investigating whether there was prolonged relief, a critical factor in patients with chronic pain. Small sample size was a common limitation of many of the studies reviewed, and, at least in one of them, a difference between groups was generated (in terms of characteristics: mean age and proportion of men and women), despite the random allocation.\textsuperscript{28}

Two of the studies included in the review did not involve a control group; however, the maintenance of a positive effect for over 30 days after the last therapeutic intervention, as it occurred in an experiment conducted by Scafani et al., makes unlikely a placebo effect.\textsuperscript{15} Conversely, a controlled study failed to demonstrate the analgesic efficacy of lidocaine in fibromyalgia patients, because the reduction in pain scores did not reach statistical significance, although more important reliefs have been obtained in the group receiving the drug, compared to placebo.\textsuperscript{16}

According to most studies reviewed, the lasting effect would be obtained after repeated infusions of the drug, although the possibility of relief after a single infusion could not be ruled out. Of the six experiments related to fibromyalgia, only two have not confirmed the analgesic power of intravenous lidocaine, having strong evidence of its efficacy for pain control in these patients.

With regard to musculoskeletal pain, the positive effects of drugs tend to be poor and generally do not improve significantly the patients’ disability nor quality of life, despite the pain relief produced.\textsuperscript{30} Thus, a greater number of studies to evaluate the effect of systemic lidocaine in these patients to determine its actual usefulness and effectiveness is still needed.

Boas et al. reported a reduction of pain by deafferentation and of central pain with the use of intravenous lidocaine, indicating a possible therapeutic value of this route for lidocaine in the management of intractable neuropathic pain syndromes.\textsuperscript{35} Since then, several studies have demonstrated that systemic lidocaine may be effective in treating various disorders that present with neuropathic pain, at doses that do not produce frank anesthesia and in plasma concentrations below those required to block axonal conduction.\textsuperscript{23,35–38} The analgesic effects of the drug may be observed in patients with diabetic neuropathy, postherpetic neuralgia and in several neuropathic disorders, such as complex regional syndrome type I and II and post-stroke pain.\textsuperscript{28}

In cases of peripheral neuropathic pain, plasma concentrations of lidocaine between 1.5-2.5 mg/mL appear sufficient to promote analgesia.\textsuperscript{29} However, there is evidence that the duration of exposure can be more important than the dose itself, leading to a reduction in VAS score for continuous pain after infusion of high (5 mg/kg) and low (1 mg/kg) doses of lidocaine for periods of two hours or more, although there was no difference from placebo.\textsuperscript{39} The fact that lidocaine has reached maximum analgesia within five minutes after the start of infusion, with an abrupt increase in its analgesic effect after a certain plasma concentration (0.62 μg/mL), suggests that its effect by venous route does not accompanies a dose-effect curve, suddenly blocking the painful stimulus.\textsuperscript{40}

Although the half-life of the drug is only 120 minutes, the analgesia provided by systemic lidocaine is prolonged, maybe extending over days or even weeks.\textsuperscript{21} This may be due to the action of intravenous lidocaine in the peripheral and central nervous system. It is known that neuromata formed at sites of injury to peripheral nerves have an abnormal accumulation of sodium channels, which should be a big contributor
<table>
<thead>
<tr>
<th>Author(s)/year</th>
<th>Sample size (cases/controls)</th>
<th>Test type (crossover/parallel/open)</th>
<th>No. of infusions of lidocaine</th>
<th>Infusion for each dose</th>
<th>Infusion time</th>
<th>Significant relief compared to placebo</th>
</tr>
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<tr>
<td>Wallace et al., 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>11 (11/11)</td>
<td>Crossover</td>
<td>1</td>
<td>*</td>
<td>*</td>
<td>Yes</td>
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<td>Baranowski et al., 1999&lt;sup&gt;19&lt;/sup&gt;</td>
<td>24 (24/24)</td>
<td>Crossover</td>
<td>2</td>
<td>1 and 5 mg/kg</td>
<td>2 h</td>
<td>No</td>
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<tr>
<td>Attal et al., 2000&lt;sup&gt;14&lt;/sup&gt;</td>
<td>16 (16/16)</td>
<td>Crossover</td>
<td>1</td>
<td>5 mg/kg</td>
<td>30 min</td>
<td>Yes</td>
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<td>Tremont-Lukats et al., 2006&lt;sup&gt;18&lt;/sup&gt;</td>
<td>32 (7/9/8/8)</td>
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<td>1</td>
<td>1, 3 e 5 mg/kg</td>
<td>6 h</td>
<td>Yes (higher dose)</td>
</tr>
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<td>Crossover</td>
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<td>5 mg/kg</td>
<td>30 min</td>
<td>Yes</td>
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<tr>
<td>Wallace et al., 2000&lt;sup&gt;22&lt;/sup&gt;</td>
<td>16 (16/16)</td>
<td>Crossover</td>
<td>1</td>
<td>*</td>
<td>*</td>
<td>Yes</td>
</tr>
<tr>
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<td>20 (10/10)</td>
<td>Crossover</td>
<td>1</td>
<td>5 mg/kg</td>
<td>30 min</td>
<td>No</td>
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<td>30 (15/15)</td>
<td>Parallel</td>
<td>4</td>
<td>3 mg/kg</td>
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<td>Schafranski et al., 2009&lt;sup&gt;15,1&lt;/sup&gt;</td>
<td>23</td>
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<td>5</td>
<td>2-5 mg/kg</td>
<td>2 h</td>
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<td>15 (8/7)</td>
<td>Crossover</td>
<td>1</td>
<td>5 mg/kg</td>
<td>30 min</td>
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<td>Kvarnström et al., 2003/2004&lt;sup&gt;27&lt;/sup&gt;</td>
<td>10 (10/10)</td>
<td>Crossover</td>
<td>1</td>
<td>2.5 mg/kg</td>
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<td>500 mg</td>
<td>60 min</td>
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<td>Crossover</td>
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<td>5 mg/kg</td>
<td>4 h</td>
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<td>Crossover</td>
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<td>5 e 7.5 mg/kg</td>
<td>4 h</td>
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<td>Crossover</td>
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<td>5 mg/kg</td>
<td>42 min</td>
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<th>Duration of effect</th>
<th>Plasma concentration at which there was relief</th>
<th>Adverse effects</th>
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<tr>
<td>Wallace et al., 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>&gt;50</td>
<td>&gt;50 (1 mg/kg) and &gt;30 (5 mg/kg)</td>
<td>1.5-2.5 µg/mL</td>
<td>Delirium, nausea</td>
<td>2</td>
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<td>Baranowski et al., 1999&lt;sup&gt;19&lt;/sup&gt;</td>
<td>~50</td>
<td>&gt;30 (5 mg/kg)</td>
<td>1,7 µg/mL</td>
<td>Perioral paraesthesia (higher dose)</td>
<td>2</td>
<td></td>
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<td>Attal et al., 2000&lt;sup&gt;24&lt;/sup&gt;</td>
<td>~50</td>
<td>10/6</td>
<td>45 min</td>
<td>Delirium, dizziness, drowsiness, dysarthritis, blurred vision, tremors, dry mouth, headache.</td>
<td>4</td>
<td></td>
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<td>&gt;30</td>
<td>19/4</td>
<td>1,5-4,1 µg/mL</td>
<td>Delirium, nausea/vomiting, diplopia, headache, tinnitus, perioral paresthesia, metallic taste, tightness in throat.</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lemming et al., 2005&lt;sup&gt;18&lt;/sup&gt;</td>
<td>~11</td>
<td>11/2</td>
<td>6 h</td>
<td>Delirium, dry mouth</td>
<td>5</td>
<td></td>
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<tr>
<td>Tremont-Lukats et al., 2006&lt;sup&gt;28&lt;/sup&gt;</td>
<td>~30</td>
<td></td>
<td></td>
<td>Delirium, dry mouth</td>
<td>5</td>
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<td>Attal et al., 2004&lt;sup&gt;21&lt;/sup&gt;</td>
<td>&gt;60</td>
<td>11/11/11</td>
<td>6 h</td>
<td>Delirium, drowsiness, perioral numbness, truncated speech, dizziness, dysarthritis.</td>
<td>5</td>
<td></td>
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<td></td>
<td>3 µg/mL</td>
<td>Delirium, nausea, paresthesia, blurred vision, dizziness, dysarthritis, headache, dry mouth.</td>
<td>4</td>
<td></td>
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<td>Gottrup et al., 2006&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Vlainich et al., 2010&lt;sup&gt;17&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>No adverse effects</td>
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<td></td>
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<td>~15 and &gt;10 (after 30 days)</td>
<td></td>
<td></td>
<td>Not applicable</td>
<td>2</td>
<td></td>
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<tr>
<td>Kastrup et al., 1987&lt;sup&gt;23&lt;/sup&gt;</td>
<td>~40 (1-3 days) and &gt;15</td>
<td>9/4</td>
<td>3-21 days</td>
<td>Drowsiness, perioral paresthesia.</td>
<td>4</td>
<td></td>
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<td>Kvarnström et al., 2003/2004&lt;sup&gt;27&lt;/sup&gt;</td>
<td>~10 (&gt;50 in 1 patient)</td>
<td>1/0</td>
<td></td>
<td>Not applicable</td>
<td>5</td>
<td></td>
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<tr>
<td>Ferrante et al., 1996&lt;sup&gt;24,27&lt;/sup&gt;</td>
<td>100 (100 patients), 62, 55 and 40 (the other)</td>
<td>13</td>
<td>0,62 µg/mL</td>
<td>Drowsiness, perioral paresthesia, headache, discomform, dry mouth, nausea, muscle spasms.</td>
<td>5</td>
<td></td>
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<tr>
<td>Gormsen et al., 2009&lt;sup&gt;26&lt;/sup&gt;</td>
<td>~36</td>
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to the severe pain produced by such lesions.\(^{14,41}\) The central hyperalgesia, on the other hand, is related to sodium channels located at the ends of mechanoreceptors, in the spinal cord, and in dorsal root ganglia.\(^{15}\) The blocking of such sodium channels cause inhibition of the spontaneous and evoked neuronal activity and reduces the neuronal hyperactivity, with greater pain relief and for a longer time, compared with that related to the drug’s pharmacokinetic patterns. Lidocaine also promotes the reduction of allodynia and hyperalgesia. A decrease in spontaneous pain, dysesthesia, mechanical hyperalgesia and mechanical allodynia occurs.\(^9\)

In addition to its well established anesthetic and antiarrhythmic actions, intravenous lidocaine also has significant anti-inflammatory properties, by inhibiting the release of cytokines and interfering with the action of inflammatory cells, such as macrophages, monocytes and polymorphonuclear cells.\(^{9,11,42}\) This latter form of action is being currently tested in several studies and seems very promising.

In patients with painful diabetic neuropathy, lidocaine can reduce spontaneous activity in small myelinated fibers by stabilizing the damaged nerve membrane; this has been proposed as the cause of neuropathic pain.\(^{23}\) Furthermore, the effect of systemic lidocaine on neuropathic pain may be different, depending on the source of pain generation. Thus, its effectiveness may be greater in patients with peripheral nerve injury than in those with pain due to damage to the CNS or of unknown etiology.\(^{29}\)

In the study by Viola et al. (2006), there was a trend for a greater response to lidocaine in doses of 7.5 mg/kg compared with 5 mg/kg, but without statistical significance.\(^{24}\) This result may indicate that the doses examined were near the top of the dose-response curve for this therapy. Although several studies confirm the efficacy of lidocaine in cases of continuous spontaneous pain caused by peripheral nerve injury, other trials failed to accordingly reaffirm the beneficial effect of the drug.

The literature suggests that, in fact, intravenous lidocaine is effective in the management of chronic pain. Ten of the 14 studies in patients with peripheral neuropathies obtained favorable outcomes with the systemic use of the drug in the treatment of diseases with neuropathic pain, including postherpetic neuralgia and painful diabetic neuropathy. The four remaining studies failed to demonstrate the analgesic effect of lidocaine, most likely due to methodological issues, for example, insufficient numbers of patients,\(^{26}\) or even the production of evoked pain shortly after the start of infusion, masking possible positive results.\(^{25}\)

In patients with CNS injury, lidocaine relieved neuropathic pain either below or at the level of the spinal lesion, suggesting an effect on the generating mechanisms of central pain, although it is not possible to determine whether the effect occurs at the spinal or brain level.\(^{43}\)

The lidocaine dose used by several investigators varies, most often from 1 to 5 mg/kg, administered over a period of 30 to 60 minutes. In several randomized clinical trials, researchers measured the plasma levels of the drug in an attempt to find a relationship between concentration and response.\(^{32,40}\) Although some authors state that the minimum plasma concentration able to produce significant analgesia is 1.5 mL/L (achieved with 2-5 mg/kg infused over 30-60 minutes),\(^{22}\) no information on the specific therapeutic concentration is available.

**Conclusion**

The intravenous infusion of lidocaine as an alternative for the treatment of chronic pain of various etiologies seems to be very promising, but further studies need to be performed.

Regarding the neuropathic or musculoskeletal pain, it is not possible to uniformly specify the most effective and safe dose of intravenous lidocaine to be used in its treatment.

**Conflicts of interest**

The authors declare no conflicts of interest.

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