Comprehensive Review

Intravenous Infusions in Chronic Pain Management

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In the United States, millions of Americans are affected by chronic pain, which adds heavily to national rates of morbidity, mortality, and disability, with an ever-increasing prevalence. According to a 2011 report titled Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research by the Institute of Medicine of the National Academies, pain not only exacts its toll on people's lives but also on the economy with an estimated annual economic cost of at least $560 - 635 billion in health care costs and the cost of lost productivity attributed to chronic pain. Intravenous infusions of certain pharmacologic agents have been known to provide substantial pain relief in patients with various chronic painful conditions. Some of these infusions are better, and although not necessarily the first therapeutic choice, have been widely used and extensively studied. The others show promise, however are in need of further investigations. This article will focus on non-opiate intravenous infusions that have been utilized for chronic painful disorders such as fibromyalgia, neuropathic pain, phantom limb pain, post-herpetic neuralgia, complex regional pain syndromes (CRPS), diabetic neuropathy, and central pain related to stroke or spinal cord injuries. The management of patients with chronic pain conditions is challenging and continues to evolve as new treatment modalities are explored and tested. The following intravenous infusions used to treat the aforementioned chronic pain conditions will be reviewed: lidocaine, ketamine, phentolamine, dexmedetomidine, and bisphosphonates. This overview is intended to familiarize the practitioner with the variety of infusions for patients with chronic pain. It will not, however, be able to provide guidelines for their use due to the lack of sufficient evidence.

Key words: Intravenous infusions in chronic pain management, bisphosphonates, phentolamine, ketamine, lidocaine, Dexmedetomidine, chronic pain

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Intravenous infusions of certain pharmacologic agents have been known to provide substantial pain relief in patients with various chronic painful conditions. Certain infusion therapies have been studied extensively, while others have very little data to support their use. Most pain practitioners are familiar with non-opiate intravenous infusions; this article will provide a current overview of the data supporting the use of various non-opioid intravenous infusions for the treatment of chronic pain conditions (Table 1).

Lidocaine

Background and Rationale

The pain-relieving properties of sodium channels blockers have been known for hundreds of years, dating back to the seventeenth century, when European settlers described using coca leaves to alleviate toothaches (1). The analgesic effect of systemic lidocaine was first reported in 1962, when Bartlett and Hutaserani (2) used an intravenous infusion to treat postoperative pain. Thirty-six years later Groudine and colleagues demonstrated that intravenous (IV) lidocaine not only decreases postoperative pain, but may also shorten the hospital stay in patients undergoing radical retropubic prostatectomy (3) (Table 2).

Although effective, the high incidence of side effects at doses required for pain control, coupled with the advent of many safer forms of analgesia, led to a decline in its use over the ensuing decades. The 1980s witnessed resurgence in the analgesic use of systemic lidocaine after the publication of a report by Boas et al demonstrating that IV lidocaine attenuated central pain, a condition often refractory to more conventional treatment (4).

Pathophysiology

Voltage-gated sodium channels are heteromeric transmembrane protein complexes consisting of one very large [alpha] subunit and one or 2 smaller ancillary [beta] subunits. Both tetrodotoxin-sensitive (Na 1.3 and 1.7) and -resistant (1.8 and 1.9) channels have been implicated in the etiology and maintenance of pain. The activation of voltage-gated sodium channels may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain. A growing body of evidence suggests that the proliferation and activation of sodium channels after nerve injury and carrageenan-induced inflammatory pain may result in ectopic discharges stemming from the site of injury, dorsal root ganglia, or even in adjacent uninjured neurons (5-7). Spontaneous discharges have been shown to develop in both myelinated and unmyelinated nerve fibers, suggesting that ectopic activity can arise in both nociceptors and low-threshold mechanoreceptors (8). In addition to spontaneous pain, preclinical evidence also supports a role for both tetrodotoxin-sensitive and -resistant sodium channels in evoked pain (9,10).

Clinical Use

It is not surprising then that controlled clinical studies have demonstrated efficacy for systemic lidocaine and its oral preparations for neuropathic and acute nociceptive pain (11-14). The plasma concentration of lidocaine necessary to relieve clinical and experimental pain is in the order of 5 – 10 μm, far less than that required to overcome nerve conduction (15). A 2006 systematic review and meta-analysis by Tremont-Lukats et al (16) reviewed randomized controlled trials on systemic administration of IV lidocaine (most commonly 5mg/kg over 30 - 60 minutes) and its synthetic oral analogues to relieve neuropathic pain, and found that these agents were superior to placebo and equal to morphine, gabapentin, amitriptyline, or amantadine for treatment of neuropathic pain. According to this review IV lidocaine is

Table 1. *Infusion agents mechanis of action.*

IV infusion agent	Mechanism of action	Potential risks and side effects
Lidocaine	Blocks sodium channels in the neuronal cell membrane that may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain	Seizures, somnolence, confusion, headache, nausea, vomiting, numbness and tingling, dizziness, metallic taste, tremor, dry mouth, insomnia, cardiac arrhythmias, hemodynamic instability
Ketamine	Antagonizes NMDA-R, which enhances sustained neuronal depolarization and contributes to increased excitatory transmission along afferent pain pathways in the dorsal horn of the spinal cord	Tachyarrhythmias, hallucinations, flashbacks, erratic behavior
Phentolamine	α-adrenergic antagonist which may have a role in treating painful conditions that respond to attenuation of sympathetic nervous system activity	Hypotension, tachycardia, cardiac arrhythmias, gastrointestinal distress
Dexmedetomidine	Selective α2-adrenergic receptor agonist which binds to transmembrane G protein-binding adrenoreceptors in the periphery and in the brain and spinal cord	Hypotension, bradycardia, respiratory depression, nausea, xerostomia, sinus arrest, transient hypertension
Bisphosphonates	Pyrophosphate analogs, suppress bone resorption via osteoclast inhibition and shorten osteoclast life span	Flu-like symptoms, acute phase reaction, osteonecrosis of the jaw

Table 2. *Published randomized, placebo-controlled or comparative trials referenced in this review for Lidocaine.*

IV infusion agent: Lidocaine					
Chronic pain condition	**Authors**	**n**	**Dose and duration of IV infusion**	**Methodology**	**Results (pain relief)**
Central Neuropathic Pain	Attal et al (17)	16	5mg/kg, 30 minutes	Crossover	Lidocaine > Placebo
	Finnerup et al (18)	24	5mg/kg, 30 minutes	Crossover	Lidocaine > Placebo
	Kvarnstrom et al (19)	10	2.5mg/kg, 40 minutes	Crossover	Lidocaine = Placebo
Chronic Daily Headache: No randomized controlled trial cited in this review					
Peripheral Neuropathic Pain	Viola et al (22)	15	5 and 7.5mg/kg, 4 hours	Crossover	Lidocaine > Placebo
	Kastrup et al (23)	15	5mg/kg, 30 minutes	Crossover	Lidocaine > Placebo
	Galer et al (24)	9	2 and 5mg/kg, 45 minutes	Crossover	No controls
	Backonja et al (25)	32	1, 3, and 5mg/kg/hr, 6 hours	Parallel	Lidocaine > Placebo
Postherpetic Neuralgia & Peripheral Nerve Injury	Attal et al (26)	24	5mg/kg, 30 minutes	Crossover	Lidocaine > Placebo
	Rowbotham (27)	19	5mg/kg, 60 minutes	Crossover	Lidocaine > Placebo
	Wallace et al (28)	11	Targeted plasma concentrations 0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml (each held for 10 minutes)	Crossover	Lidocaine > Placebo
	Baranowski et al (29)	24	1 and 5 mg/kg, 2 hours	Crossover	Lidocaine = Placebo
CRPS	Wallace et al (30)	16	targeted plasma concentrations 1, 2, and 3 μg/ml, 20 minutes	Crossover	Lidocaine = Placebo
	Tremont-Lukats et al (31)	32	1, 3, and 5 mg/kg, 6 hours	Parallel	Lidocaine > Placebo at 5mg/kg dose
PPSP	Grigoras et al (33)	36	1.5mg/kg bolus followed by 1.5mg/kg/hr, duration of surgical procedure; stopped one hour after skin closure	Parallel	Lidocaine > Placebo
	Wu et al (34)	32	1mg/kg bolus followed by 4 mg/kg, 40 minutes	Crossover	Lidocaine > Placebo: Stump pain Lidocaine = Placebo: Phantom limb pain
Fibromyalgia	Sorensen et al (35)	12	5mg/kg, 30 minutes	Crossover	Lidocaine = Placebo

n = No. of participants

efficacious in providing pain relief to patients with neuropathic pain related to diabetes, trauma, and cerebrovascular disease but was found to be ineffective against plexopathy from tumor infiltration and HIV-related polyneuropathy. Tremont-Lukats et al also indicate that lidocaine's short serum half-life of 120 minutes make it impractical for chronic pain use and state that pain relief with lidocaine has been measured within 24 hours in all trials because in most patients the effect disappears a few hours after treatment (16).

Central Neuropathic Pain

Several studies investigating the role of lidocaine in the treatment of central neuropathic pain seen in spinal cord injury stroke have been conducted. Attal et al (17) conducted a double-blind placebo controlled study in crossover fashion to investigate the effects of systemic administration of lidocaine on different components of neuropathic central pain by quantitative sensory testing. Intravenous lidocaine 5 mg/kg or placebo 0.9% saline was infused for 30 minutes in 16 patients with chronic post-stroke (n = 6) or spinal cord injury (n = 10), including patients with the following conditions: syringomyelia, post-traumatic myelomalacia, and cervical spondylosis with myelopathy-related pain. This was followed by post-infusion testing on both spontaneous ongoing pain (at or below level of injury) and evoked pains including allodynia and hyperalgesia (17). This study reports the efficacy of IV lidocaine in reducing the intensity of spontaneous ongoing pain and the intensity of brush-induced allodynia and static (punctate) mechanical hyperalgesia. IV lidocaine was also

shown to be less effective against thermal allodynia and hyperalgesia.

Finnerup et al (18) conducted a similar study to investigate the analgesic effect of IV lidocaine on neuropathic pain in patients with spinal cord injury assessed using a (VAS) and quantitative sensory testing. In this randomized, controlled, double-blind crossover trial, 24 spinal cord injury patients with neuropathic pain at or below the level of injury were infused with IV lidocaine 5mg/kg and placebo over 30 minutes. Similarly this study reported reduced spontaneous pain in all patients, significantly relieved at-level and below-level neuropathic pain, as well as reduced brushed-evoked dysesthesia. IV lidocaine was not effective against cold allodynia, pinprick hyperalgesia, or pain evoked by repetitive pinprick (18). Kvarnstrom et al (19) also investigated the analgesic effect of IV lidocaine on neuropathic pain following traumatic spinal cord injury with pain at or below the level of injury utilizing a VAS for pain rating and sensory function and quantitative measurement of temperature thresholds. A randomized, double-blind, 3 period, 3-treatment, cross-over design study was conducted with 10 spinal cord injury patients including partial or complete injuries at the cervical, thoracic, or lumbar level. Lidocaine 2.5 mg/kg infused over 40 minutes was investigated with results demonstrating that lidocaine did not change temperature thresholds or mechanical, dynamic, and static susceptibility (19). In comparison to the aforementioned studies, Kvarnstrom et al (19) studied a lower concentration of IV lidocaine, which may account for the discrepancy witnessed between these studies.

Chronic Daily Headache

The efficacy of IV lidocaine on the effect of chronic daily headache (CDH) is limited. There is scarce evidence due to the lack of randomized prospective clinical trials. Williams and Stark (20) studied the efficacy of IV lidocaine infusion for chronic daily headache in a retrospective survey of 71 consecutive patients admitted for lidocaine infusion for the treatment of treatment of CDH (90% of patients with history of migraine headache) with substantial medication overuse. The most commonly reported overused medications were opioids including oral and IV forms, followed by ergotamine-containing medications. Admitted study patients received IV lidocaine infusions of 2 mg per minute for a mean of 8.7 days, permitting 97% of patients to be successfully withdrawn from the offending analgesic agent (20). At the time of hospital discharge 90% of patients reported absence or improvement of their daily headache; at one-month follow-up 76% of patients reported absence and improvement of daily headache with 88% of patients free of offending analgesic agents. Correspondingly at 6 months follow-up, 70% of patients reported absence or improvement of daily headache with 72% of patients free of the offending analgesic agents (20).

In an open-label, retrospective, uncontrolled study of IV lidocaine for 68 patients with intractable headache in an inpatient setting, Rosen et al (21) concluded that prolonged IV lidocaine infusion may be effective in CDH to decrease or eliminate pain and improve function. In this study, IV lidocaine was started at an infusion rate of 1 mg/minute for 4 hours on average, after which it was raised to 2 mg/minute with some patients on rates as high as 4 mg/minute. The mean length of treatment was 8.5 days with pretreatment headache scores averaging 7.9 on an 11-point scale, and posttreatment scores averaging 3.9, demonstrating an average change of 4 (21). The role of IV lidocaine for the treatment and management of CDH may be of benefit but needs to be studied further.

Peripheral Neuropathic Pain

The use of lidocaine for the treatment of peripheral neuropathic pain has been studied extensively. Viola et al (22) examined the effectiveness of IV lidocaine in 15 patients with intractable painful diabetic neuropathy in a double-blind, placebo-controlled crossover trial, in which 2 doses of IV lidocaine (5 and 7.5 mg/kg) versus saline were infused over 4 hours at 4 weekly intervals. Outcomes were assessed using the McGill Pain Questionnaire (MPQ), a daily pain diary, hours of sleep, fasting blood glucose, and the use of other pain-relieving medications. Both doses studied significantly reduced the severity of pain compared to placebo ($P < 0.05$ to $P < 0.001$ for the different measures), which remained decreased at both 14 and 28 days after the infusion (22). There were no significant differences seen between IV lidocaine groups and the saline placebo group in the mean fasting blood glucose levels, mean hours of sleep, and the mean daily pain scores recorded in the daily journal.

Kastrup et al (23) also studied the effect of IV lidocaine (5 mg/kg infused over 30 minutes) on 15 patients with painful neuropathy in a prospective randomized, placebo controlled crossover study with 5-week washout. Pain was assessed utilizing Functional Independent Staging (FIS) and VAS scores with results

showing significantly less pain in the lidocaine treated patients. The duration of pain relief was 14 days with using the FIS and 3 days using VAS (23). Galer et al (24) demonstrated statistically significant decreased pain scores for utilizing a lower dose of IV lidocaine infusion of 2 mg/kg over 45 minutes in 9 patients (n = 5; diabetic polyneuropathy, n = 2; other polyneuropathy; n = 2; nerve injury, and n = 1; lumbosacral arachnoiditis) in a randomized prospective double-blind study in crossover fashion with one week washout without controls.

Backonja and Tremont-Lukats (25) in a prospective placebo controlled study (n = 32) studied the effect of 3 different IV lidocaine dosages (1, 3, and 5mg/kg/hr) infused over 6 hours for the treatment of peripheral neuropathic pain. Post-hoc analysis showed that lidocaine 5mg/kg/hr significantly decreased pain scores over placebo at hour 6 (P = 0.05), and 10h (P = .009) of IV treatment (25).

Postherpetic Neuralgia and Peripheral Nerve Injury

Attal et al (26) in a double-blind placebo-controlled crossover study with 2-week washout evaluated the effect of IV lidocaine (5 mg/kg infused over 30 minutes) on spontaneous and evoked pain (allodynia and hyperalgesia) in 22 patients with peripheral nerve injury (trauma, n = 14; postherpetic neuralgia, n = 8). Lidocaine reduced ongoing pain for up to 6 hours with a peak effect 60 to 120 minutes after infusion. A decrease in spontaneous pain, mechanical dynamic allodynia, static (punctate) mechanical allodynia, and hyperalgesia was also demonstrated. There was no significant difference in thermal allodynia and hyperalgesia noted between saline placebo and lidocaine (26). Rowbotham et al (27) also noted a decrease in VAS pain scores after IV lidocaine 5 mg/kg infused over 60 minutes in prospective, randomized, placebo-controlled crossover study of 19 patients with postherpetic neuralgia (PHN). Wallace et al (28) in a double-blind, placebo-controlled crossover study with one week washout looked at the effect of IV lidocaine infusions targeted to plasma concentrations of 0.5, 1.0, 1.5, 2.0, and 2.5 µg/mL (each held for 10 minutes) in reducing pain scores and allodynia of 11 patients with neuropathic pain from peripheral nerve injury. Lidocaine, at concentrations greater than or equal to 1.5 µg/ml, reduced VAS pain scores and area of mechanical allodynia with a return to baseline pain levels at the next measure interval which was day 7 (28).

Baranowski et al (29) investigated the effect of IV lidocaine in the pain and allodynia of PHN of 24 patients using a randomized, double-blind crossover study. Two doses of IV lidocaine (1 mg/kg and 5 mg/kg infused over 2 hours) were studied with outcomes measured at intervals during the infusion via the MPQ short form, VAS, free plasma lidocaine levels, and area of allodynia as mapped by brush stroke. In contrast to the other mentioned studies, this study showed no difference in spontaneous pain and evoked pain between placebo and IV lidocaine at both 1 mg/kg and 5 mg/kg. Lidocaine did, however, decrease the area of allodynia by 65% and 85%, respectively (29).

Complex Regional Pain Syndrome

Wallace et al (30) studied the effects of IV lidocaine on acute sensory thresholds within the painful area as well as the size of the painful area of 16 patients with complex regional pain syndrome (CRPS) I and II. In this randomized, double-blind, placebo-controlled crossover study, each patient received IV lidocaine infusions for 20 minutes at 3 targeted plasma levels (1, 2, and 3 µg/ml). Spontaneous and evoked pain scores and neurosensory testing within the painful area were measured at baseline and at each plasma level. Thermal thresholds, tactile thresholds, and the area of allodynia to punctate, stroking, and thermal stimuli were measured as part of the neurosensory testing. A significant reduction in cool-evoked pain in the allodynic areas at all 3 lidocaine concentration levels was reported with no significant effect in spontaneous pain, or pain evoked by hot, stroking, or von Frey's hairs (30). Intravenous lidocaine had no effect on cool, warm, or cold pain thresholds except at the highest concentration, which caused a significant elevation of the hot pain thresholds in the painful area (30). The authors of this study concluded that IV lidocaine affects pain in response to cool stimuli more than mechanical pain in this patient population with neuropathic pain.

Tremont-Lukats et al (31) conducted a double-blind, randomized, placebo-controlled parallel study of 32 patients with peripheral neuropathic pain of which 23 had CRPS (of whom 5 had CRPS-II) to study the effects of IV lidocaine for the relief of ongoing neuropathic pain. Patients were randomly allocated into one of 4 treatment arms, which included saline placebo or lidocaine at 1, 3, and 5 mg/kg to be infused over 6 hours without a loading dose. Pain was rated using the VAS before treatment, hourly for 6 hours, at 8 hours, and 10 hours from the initiation of the infusion and the primary outcome measure was relief of pain intensity (percentage pain intensity differ-

ence [PID %]). A significant difference in the median PID% between the 5 mg/kg group and placebo group was demonstrated with initiation of effect at 4 hours with duration until the conclusion of the study at 10 hours (31). There was no difference in relieving pain between placebo and the lower concentrations of lidocaine (1 and 3 mg/kg). In this study the authors report a decrease in pain intensity with IV lidocaine, demonstrating a decrease in spontaneous pain that was not shown in the previously mentioned studies. In a retrospective study of 49 patients severely affected by CRPS who were treated with an IV lidocaine protocol that consisted of a gradual upward titration to a blood level of 5 mg/L over a 5-day period in a monitored setting, Schwartzman et al (32) revealed that 76% of patients reported at least a 25% reduction of pain at 3 months base on a numerical rating scale (NRS), while 31% had greater than 50% pain reduction. The remaining 24% of patients expressed little benefit at 3 months. In this study there was a statistically significant improvement in all pain parameters including dynamic and static mechano-allodynia, deep muscle pain, joint pain, and thermal allodynia (cold stimulus) with moderate improvement noted in the movement disorder. Pain scores were significantly improved for approximately 3.2 months with CRPS factors returning to baseline thereafter. Despite the fact that patients were infused with IV lidocaine over a 5-day period, only minimal side effects and no severe complications were noted for all participants in the study (32). Since this was a non-randomized retrospective study with a small sample size, more studies are needed to confirm these results and to investigate the use of lidocaine in the treatment of CRPS.

Persistent Postsurgical Pain

Grigoras and colleagues (33) conducted a randomized, double-blind, placebo-controlled study to evaluate the impact of IV lidocaine on acute and persistent postsurgical pain (PPSP), analgesic requirements, and sensation abnormalities in patients undergoing surgery for breast cancer. Thirty-six patients received a bolus of IV lidocaine 1.5 mg/kg followed by a continuous infusion of lidocaine 1.5 mg/kg/h (lidocaine group) or an equal volume of saline (control group) prior to the induction of general anesthesia and stopped one hour after skin closure. Two (11.8%) patients in the lidocaine group and 9 (47.4%) patients in the control group reported PPSP at 3 months follow-up (P = 0.031). MPQ revealed greater present pain intensity in the control group (14.6 ± 22.5 vs. 2.6 ± 7.5; P = 0.025). Secondary hyperalgesia (area of hyperalgesia over length of surgical incision) was significantly less in the lidocaine group compared with control group (0.2 ± 0.8 vs. 3.2 ± 4.5 cm; P = 0.002) (33). The authors concluded that IV perioperative lidocaine decreases the incidence and severity of PPSP after breast cancer surgery. Prevention of the induction of central hyperalgesia is a potential mechanism.

Wu et al (34) in a randomized double-blind placebo controlled, crossover study investigated the efficacy of IV lidocaine infusion (1mg/kg bolus followed by 40 minute 4 mg/kg infusion) on post-amputation pain of 32 patients (stump pain alone, n = 11; phantom pain alone, n = 9; both, n = 11). The authors concluded that lidocaine significantly reduced stump pain (P < 0.01) but not phantom pain (P > 0.05) on computerized VAS scores (34).

Fibromyalgia

Sorensen et al (35) showed an improvement in VAS pain scores during and 15 minutes after a 30-minute infusion of 5 mg/kg of IV lidocaine in a double-blind placebo-controlled crossover study of 12 fibromyalgia patients. Three of the patients that responded to IV lidocaine had a reduction in pain for 4 - 7 days. The authors reported no statistically significant differences in tender points, muscle strength (hip flexors and hand grip), and muscle endurance after placebo or after IV lidocaine. The lidocaine group also exhibited a significant increase in muscle strength of wrist dorsiflexors (35).

Raphael et al (36) conducted a prospective study of the adverse effects of IV lidocaine in 106 patients with fibromyalgia as well as a retrospective questionnaire study of the efficacy of IV in 50 patients with fibromyalgia. Serial infusions of IV lidocaine were administered for 6 consecutive days at 5 mg/kg minus 100 mg and increased by 50 mg per day to 5 mg/kg plus 150 mg over 6 hours with the maximum allowable dose being 550 mg. Pain was measured on the 11-point NRS, a 4-point verbal scale of pain severity (none, mild, moderate, severe), and average hours per day in pain. Pain relief was also measured on the 11-point NRS and the duration of pain relief was also measured. Psychological and sociological dimensions of the pain and its relief were addressed by measurement of depression, coping ability, dependency, sleep, social life, work, housework,

mobility, driving, and sex life represented using the 11-point scales. Pain score, pain relief interruption, mean daily duration of pain, and verbal assessment of pain were all significantly reduced following lidocaine treatment. The mean duration of pain relief was 11.5 ± 6.5 weeks, range 0 – 36 weeks (36). Psychosocial measures improved significantly after lidocaine treatment in all parameters except work status.

Schafranski et al (37) in an open trial showed similar results after 5 sequential IV lidocaine infusions with rising dosages (2 - 5 mg/kg, days 1 - 5). Fibromyalgia Impact Questionnaire (FIQ) and a VAS for pain were applied before the first lidocaine infusion, immediately after the fifth infusion, and 30 days after the fifth infusion. Significant reductions were seen in both FIQ and VAS after the fifth infusion and were maintained after 30 days (37).

Potential Risks and Side Effects

Intravenous lidocaine is associated with significant dose-related side effects including dizziness, sedation, tinnitus, and, in higher doses, seizures and arrhythmias. The use of mexiletine, an oral lidocaine analog, generally involves a long titration schedule, and is limited by a high incidence of nausea and sedation.

Tremont-Lukats et al (16) reviewed 27 randomized double-blind, controlled clinical trials for chronic neuropathic pain, of which 13 used IV infusions of lidocaine at varying concentrations and time frames ranging from one minute to 6 hours. The most common side effects encountered in the review were metallic taste, tremor, dry mouth, insomnia, allergic reactions, and tachycardia. Serious adverse events that are known risks of IV lidocaine use, such as cardiac arrhythmias and hemodynamic instability, were notably absent from these trials. Other potential adverse effects associated with lidocaine include seizures, somnolence, confusion, headache, nausea, vomiting, numbness and tingling, and dizziness. Lidocaine should only be given intravenously to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Other barriers for lidocaine use are impracticability of IV infusion on a long-term treatment basis as well as the fact that repeated infusions may not result in prolonged pain relief.

The antiarrhythmics tocainide and flecainide, which have also been shown in clinical trials to be effective for neuropathic pain (38,39), have been implicated in cardiac arrhythmia-related fatalities. Consequently, although a study demonstrated efficacy for oral flecainide in 15 patients with PHN who responded positively to a blinded IV infusion (38), these drugs are rarely used clinically.

Ketamine

Background and Rationale (Table 3)

It is common knowledge that the excitatory amino acid glutamate is involved in acute and chronic pain pathways. Initiated by tissue injury, the excitatory signals transmitted through afferent neurons in the spinal cord and periphery are mediated primarily via the fast-inactivating kainate and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) subtypes of the glutamate receptor. Once painful stimuli of longer duration and greater intensity ensue, the accumulation of prolonged, slowly depolarizing action potentials results in the removal of the tonic Mg2+ block from the N-methyl-d-asparate (NMDA) glutamate receptor.

Pathophysiology

Activation of the NMDA receptor (NMDA-R) enhances sustained neuronal depolarization, thereby contributing to increased excitatory transmission along afferent pain pathways in the dorsal horn of the spinal cord, a process known as wind-up. The NMDA-R has also been implicated as playing a key role in neuroplasticity, long-term potentiation, and opioid tolerance (40-42). Prolonged activation of NMDA-R results in alterations in cellular signaling pathways that accentuate the responsiveness of nociceptive neurons, a phenomenon known as central sensitization. Prolonged NMDA-R stimulation can also lead to functional antagonism of opioid analgesic effects.

The NMDA-R complex is one of several ligand-gated ion channels that permit diffusion of sodium and potassium channels upon activation. Unlike other ionotropic glutamate channels, activation of NMDA-R also allows passage of calcium ions, which can affect intracellular signal processing (43). The NMDA receptor ion channel is a heterotetrameric structure that consists of up to 7 subunits (44). These include a pore-forming NR-1 subunit that binds glycine, at least one glutamate-binding NR-2 subunit, and in some cases another glycine-binding NR-3 complex. Present within the various subunits are numerous allosteric binding sites that influence function, including a zinc binding site, a proton sensor, and a polyamine site that serves to shield

Table 3. *Published randomized, placebo-controlled or comparative trials referenced in this review for Ketamine, Phentolamine, Dexmedetomidine, and Bisphosphonates.*

Chronic pain condition	Authors	n	Dose and duration of IV infusion	Methodology	Results (pain relief)
IV infusion agent: Ketamine					
Central Neuropathic Pain	Eide et al (45)	9	bolus 60 μg/kg, 6 μg/kg/min, 17-21 minutes	Crossover	Ketamine > Placebo
	Kvarnstrom et al (46)	10	0.4 mg/kg, 40 minutes	Crossover	Ketamine > Placebo
Peripheral Neuropathic Pain	Eichenberger et al (47)	20	0.4 mg/kg, over 1 hour	Crossover	Ketamine > Placebo
	Jorum et al (48)	12	60 μg/kg bolus, followed by 6 μg/kg/min infusion, 20 minutes	Crossover	Ketamine > Placebo
	Felsby et al (49)	10	0.2 mg/kg bolus over 10 minutes, followed by 0.3 mg/kg/hr, one hour or less	Crossover	Ketamine > Placebo
	Leung et al (50)	12	targeted to plasma concentrations of 50, 100 and 150 ng/ml, 20 minutes	Crossover	Ketamine = Placebo
Postherpetic Neuralgia and Peripheral Nerve Injury	Eide et al (51)	8	0.15 mg/kg, 10 minutes	Crossover	Ketamine > Placebo
	Gottrup et al (52)	20	0.24 mg/kg, 30 minutes	Crossover	Ketamine > Placebo
CRPS	Sigtermans et al (54)	60	titrated to effect from a minimum dose of 5 mg/hr to a maximum dose of 30 mg/hr, 4.2 days	Parallel	Ketamine > Placebo
	Schwarztman et al (55)	19	25 mg/hr for 4 hours daily, 10 days	Parallel	Ketamine > Placebo
Fibromyalgia	Graven-Nielsen et al (58)	29	0.3 mg/kg, 30 minutes	Crossover	Ketamine > Placebo
	Sorensen et al (35)	11	0.3 mg/kg, 10 minutes	Crossover	Ketamine > Placebo
	Noppers et al (59)	24	0.5 mg/kg, 30 minutes	Parallel	Ketamine = Placebo
Cancer Pain	Mercadante et al (60)	10	0.25 and 0.5 mg/kg, 30 minutes	Crossover	Ketamine > Placebo
IV infusion agent: Phentolamine					
CRPS	Galer (79)	37	35, 50, 75 mg, 30 minutes		
	Raja et al (80)	20	25-35 mg, in 3-8 minute intervals in increasing doses (1,2,4,8,10,10)	Crossover	Phentolamine > Placebo
IV infusion agent: Dexmedetomidine					
Analgesia in healthy controls; cold pressor test	Hall et al (98)	7	0.2 or 0.6 μg/kg/hr, 50 minutes	Crossover	Dexmedetomidine > Placebo
IV infusion agent: Bisphosphonates					
CRPS	Robinson et al (105)	27	60 mg pamidronate	Parallel	Pamidronate > Placebo
	Varenna et al (106)	82	100 mg neridronate in 2 hours, given 4 times over 10 days	Parallel	Neridronate > Placebo
	Varenna et al (107)	32	300 mg clodronate, 10 days	Parallel	Clodronate > Placebo

n = No. of participants

the proton sensor when occupied. The binding site for magnesium lies within the ion channel and magnesium blocks receptor activation under resting conditions. Within the same ion channel, there is also a site that binds numerous noncompetitive antagonists used in clinical practice such as ketamine, dextromethorphan, amantadine, and memantine.

Clinical Use

Central Neuropathic Pain

Eide et al (45) in a randomized, double-blind, placebo controlled, crossover study studied the role of NMDA receptors in the pathogenesis of central pain in 9 patients with central dysesthesia pain after spinal cord injury. An IV infusion of ketamine 6 µg/kg/min after a bolus dose of 60 µg/kg for 17 - 21 minutes was administered. Pain was evoked by non-noxious stimulation of the skin (allodynia) and by repeated pricking of the skin (wind-up-like pain). The severity of continuous and evoked pain was examined before and after ketamine treatment. The authors concluded that continuous and evoked pain was distinctly reduced by ketamine with no significant change in thresholds for the sensation of heat pain. Kvarnstrom et al (46) demonstrated that IV ketamine infusion 0.4 mg/kg over 40 minutes has significant analgesic effect in patients with neuropathic pain after spinal cord injury in a randomized, double-blind, 3 period, 3-treatment, cross-over study of 10 patients. Outcomes were measured via pain rating using the VAS, sensory function assessment with a combination of traditional sensory tests and quantitative measurement of temperature thresholds. A 50% reduction in VAS scores for spontaneous and ongoing pain during ketamine infusion, which was labeled as response to treatment, was seen in 5/10 patients (46). Ketamine did not change temperature thresholds or other changes of sensory function.

Peripheral Neuropathic Pain

Eichenberger et al (47) investigated 20 patients with chronic phantom limb pain treated with IV ketamine infusion alone (n = 10, only 10 patients received ketamine alone), IV ketamine combined with IV calcitonin, IV calcitonin alone, and placebo (0.9% saline) to study the effectiveness of calcitonin combined with ketamine in treating chronic phantom limb pain. The intensity of phantom pain measured via VAS was recorded before, during, at the end, and 48 hours after each infusion. Pain thresholds after electrical, thermal, and pressure stimulation were recorded before and during each infusion. After conducting this randomized, double-blind, crossover study, the authors reported that IV ketamine infusion (0.4 mg/kg, over one hour), but not calcitonin alone, reduced phantom limb pain. Ketamine in combination with calcitonin was reported not to be superior to ketamine alone. There was no difference in basal pain thresholds between the amputated and contralateral side, except for pressure pain. The analgesic effect of the combination of calcitonin and ketamine was associated with a significant increase in electrical thresholds, but with no change in pressure and heat thresholds. Only the combination of the 2 drugs significantly reduced mean and maximal pain intensity 48 hours after treatment compared with placebo (47).

Jorum et al (48) in a randomized double-blind, placebo controlled, crossover study examined the effect of IV ketamine infusion (60 µg/kg bolus, followed by 6 µg/kg/min infusion over 20 minutes) on thermal allodynia/hyperalgesia, ongoing pain, and mechanical allodynia/hyperalgesia in patients with neuropathic pain (post-traumatic neuralgia, n = 11; PHN, n = 1) known to experience severe cold allodynia. Alfentanil was used as an active control in this study and psychophysical testing was started approximately 8 minutes after the start of bolus and infusion. Ketamine-treated patients had reduced hyperalgesia to cold pain, demonstrated by a reduction of VAS score to cold stimulation at threshold level, but did not significantly alter the threshold for cold pain detection. Ketamine reduced the radiation of pain from the site of cold stimulation and significantly diminished mechano-allodynia to brush-stimulation (48). Ketamine treated patients also had a reduced VAS score for spontaneous pain.

Felsby et al (49) in a double-blind, placebo-controlled study of 10 patients with peripheral neuropathic pain treated with ketamine (0.2 mg/kg bolus over 10 minutes, followed by 0.3 mg/kg/hr for one hour or less) reported a significant reduction of spontaneous pain as well as a significant reduction of the area of allodynia. Ongoing pain determined by VAS score, area of touch-evoked allodynia, and detection of and pain thresholds to mechanical and thermal stimuli were measured before and during drug infusion. Detection of and pain thresholds to mechanical and thermal stimuli were not significantly changed by IV ketamine infusion (49).

Leung et al (50) concluded that ketamine had no effect on spontaneous pain in a randomized, double-blind, controlled, crossover study of 12 patients with post-nerve injury neuropathic pain characterized by

allodynia and hyperalgesia treated with IV ketamine infusions (targeted to plasma concentrations of 50, 100, and 150 ng/ml for 20 minutes). Neurosensory testing that included thermal thresholds, thermal pain and von Frey filament thresholds, and spontaneous and evoked pain scores were obtained at the beginning of each infusion and each targeted plasma level. Ketamine infusion-treated patients showed no significant change in cold pain thresholds as well as no significant effect on warm or hot pain thresholds. Ketamine also showed no significant effects on the von Frey hair stimulation threshold (50). The authors did report however, that ketamine demonstrated a significant reduction in the von Frey evoked allodynic area in 2 patients with cold allodynia.

PHN and Peripheral Nerve Injury

Eide et al (51) examined the analgesic effects of ketamine (0.15 mg/kg, over 10 minutes) in 8 patients with PHN in a randomized, double-blind crossover study. The effects of ketamine treatment on pain relief, allodynia, wind-up-like pain, and tactile and temperature threshold were measured between 10 and 45 minutes after infusion. Ketamine infusion treated patients did not experience significant change on thresholds for warm, cold, heat pain, or tactile sensation. However, ketamine did produce significant relief of spontaneous pain, pain evoked by non-noxious stimulation of the skin (allodynia), and wind-up-like pain (51). Gottrup et al (52) studied the effects of IV infusion of ketamine (0.24 mg/kg, over 30 minutes) on spontaneous pain, brush-evoked pain, and pinprick-evoked pain in 20 patients with nerve injury pain. In this randomized, double blind, placebo-controlled, crossover study, the authors demonstrated a significant reduction in ongoing pain measured every 10 minutes for 40 minutes post infusion and evoked pain to brush and pinprick.

CRPS

Clinical studies have evaluated the use of NMDA-R antagonists for a wide array of chronic pain conditions. Many of these studies support the use NMDA-R antagonists for the treatment of chronic pain but further study is required to validate the therapeutic role of NMDA-R antagonists in this setting. Kiefer et al (53) conducted a nonrandomized open-label trial to investigate the efficacy of ketamine in anesthetic dosage in patients with refractory CRPS who had failed available standard therapies. Twenty patients with refractory CRPS were treated with a 5-day continuous infusion of ketamine initiated at 3 mg/kg/hr titrated up daily to a final dose of 7 mg/kg/hr. All 20 patients were deeply sedated for the duration of treatment with 17 of the 20 patients electively intubated for airway protection and placed on a ventilator for the entire duration of treatment. Following ketamine treatment, significant pain relief measured by NRS was observed at one, 3, and 6 months (93.5 ± 11.1%, 89.4 ± 17.0%, 79.3 ± 25.3%; $P < 0.001$) (53). At one month, complete remission was seen in all the study patients, at 3 months in 17, and at 6 months in 16 patients with significant pain relief observed in the remainder of patients with relapse at 3 and 6 months. The authors also reported a significant improvement of the movement disorder, ability to perform activities of daily living, and the ability to work in concert with the decrement in pain.

In a double-blind, randomized, placebo-controlled parallel-group trial of 60 CRPS-I patients treated with sub-anesthetic IV ketamine infusion for 4.2 days, Sigtermans et al (54) showed significant spontaneous pain relief without functional improvement. Patients were treated with placebo (n = 30) or a low dose IV infusion of ketamine (n = 30), which was titrated to effect from a minimum dose of 5 mg/hr to a maximum dose of 30 mg/hr. The authors reported significant reduction in spontaneous pain that was maintained for 11 weeks (54). Schwarztman et al (55), in another randomized, double-blind, placebo controlled study of 19 CRPS patients treated as outpatients with a low dose 10 day infusion of ketamine (25 mg/hr for 4 hours daily), were also able to demonstrate a significant reduction in many pain parameters. The participants of this study were followed 2 weeks prior to infusion, at 2 weeks post-infusion, and then monthly for 3 months after the last infusion at day 10, with outcomes measured by the short form MPQ, quality of life, activity watch, and pain questionnaires weekly for 3 months. Two weeks pre-treatment, and one- and 3-month post-treatment thermal detection thresholds, thermal pain, dynamic and static mechano-allodynia, deep pressure pain thresholds, quantification of motor function, and cutaneous temperature were also measured. The authors of this study found a statistically significant reduction of pain ($P < 0.05$) in the ketamine treated group as measured by (1) the MPQ for the duration of the study; (2) in several of the parameters evaluated in the pain questionnaire which included: pain in the affected area, burning pain, pain when touched or brushed lightly, and overall pain level; (3) the activity watch demonstrated fewer nighttime awakenings as

well as lower daytime pain scores; and (4) spontaneous burning pain decreased ($P < 0.05$) for one month (55). Changes in the following parameters (1) overall pain, (2) deep muscle pain, (3) joint pain, (4) quantitative sensory testing, and (5) quality of life issues, did not reach statistical significance ($P > 0.05$) but trended toward improvement in the ketamine-treated group (55).

Goldberg et al (56) in an open label, prospective, pain journal evaluation of a 10-day infusion of IV ketamine at 40 mg lasting 4 hours and increased to a maximum of 80 mg over 10 days in 40 CRPS patients also demonstrated a significant reduction in pain. Pain journal analysis showed a significant reduction ($P < 0.001$) in worst daily pain as patient's ability to initiate movement showed significant improvement ($P = 0.012$) by the tenth day of infusion (56).

Other observational studies investigating the effects of IV ketamine in patients suffering from CRPS have shown similar results. Correll et al (57), in a retrospective study of patients (n = 33) with CRPS treated with a second infusion of IV ketamine with mean dose of 23.4 mg/hr (range 10 - 50 mg/hr) for a mean of 4.7 days (range 1 - 20 days), demonstrated that these patients had longer periods of pain relief than patients treated with a single infusion of ketamine. Following the first ketamine infusion, as measured by the verbal numeric pain scores, 54% of 33 subjects remained pain free at 3 months and 31% remained pain free at 6 months (57). After a second infusion of ketamine, 58% of 12 patients experienced relief at one year, while almost 33% remained pain free at 3 years (57). The use of ketamine infusions for the treatment of CRPS shows promise but further studies are needed, especially prospective, randomized, double-blind placebo-controlled studies of anesthetic and sub-anesthetic doses of ketamine infusions.

Fibromyalgia

Graven-Nielsen et al (58) investigated the efficacy of IV ketamine infusion (0.3 mg/kg given over 30 minutes on 2 separate occasions one week apart) on fibromyalgia syndrome (FMS) patients. In this randomized, double-blind, crossover study 29 FMS patients were treated with ketamine or placebo (isotonic saline) to determine which patients responded to ketamine treatment (0.5% reduction in pain intensity at rest on 2 consecutive VAS assessments). Fifteen out of 17 ketamine-responders were included in the second part of the study, which involved the same ketamine or saline placebo on 2 separate occasions one week apart. Prior to treatment infusion, and 10, 20, and 30 minutes after infusion start, patient VAS scores of ongoing pain were measured with somatosensory sensibility assessments (pressure algometry, cutaneous and intramuscular electrical stimulation, and saline-induced muscle pain). The results of this study reported that the ketamine infusion compared with placebo infusion reduced VAS scores of muscular pain at rest, local and referred pain areas, the span between the pain threshold to single and repeated intramuscular stimuli, and increased the mean pressure pain tolerance (measured by 3 pairs of tender points) (58). Ketamine did not have a significant effect on pain threshold to single intramuscular electrical stimulation. The authors of this study concluded that muscular hyperalgesia and muscle pain at rest were reduced by ketamine infusion.

Sorensen et al (35) in a double blind placebo controlled study of 11 patients with fibromyalgia studied the efficacy of IV ketamine (0.3 mg/kg over 10 minutes as a single dose) during a one-week period. A significant reduction of pain at the end of the ketamine injection ($P < 0.05$) and 20 - 80 minutes after the end of the injection compared to placebo ($P < 0.0l - P < 0.001$) as measured by VAS was noted (35). Statistically significant differences were seen in pressure pain threshold and pain tolerance at tender points, control points, and muscle endurance, with no statistically significant differences in muscle strength after ketamine or placebo reported.

Noppers et al (59) studied 24 fibromyalgia patients treated with an IV infusion of ketamine (0.5 mg/kg over 30 minutes, n = 12) or placebo (midazolam 5 mg, n = 12) in a randomized double blind, active placebo-controlled trial and concluded that short-term infusion of ketamine is insufficient to induce long-term analgesic effects in these patients. The study patients were followed for 8 weeks with initial VAS score and FIQ measured for 2.5 hours post-infusion and weekly. Fifteen minutes post-infusion the number of patients showing a reduction in pain scores > 50% was 8 in the treatment group vs. 3 in the control group ($P < 0.05$), at t = 180 minutes, 6 vs. 2 (not statistically significant), at the end of the first week, 2 vs. 0 (nonsignificant), and at end of the eighth week, 2 vs. 2 in the ketamine and midazolam groups, respectively (59).

Cancer Pain

Mercadante et al (60) in a randomized, double-blind, crossover study of 10 cancer patients with

neuropathic pain unrelieved by morphine compared subhypnotic doses of single-day 30-minute IV infusions of ketamine (0.25 and 0.5 mg/kg) with placebo (saline). Pain intensity on a 0 to 10 numerical scale was measured after 30, 60, 120, and 180 minutes following ketamine infusion with findings of significant pain intensity reduction with both doses, with the higher dose showing greater pain relief. Pain relief persisted over the 180-minute observation period at both ketamine infusion doses (60).

Potential Risks and Side Effects

Ketamine produces a state of dissociative anesthesia, with amnesia and analgesia as primary components. There is also a possibility of tachy-arrhythmias, hallucinations, flashbacks, and erratic behavior, which are usually seen at higher doses. Ketamine is the most effective and well-studied NMDA-R antagonist, but it is routinely available only in an IV formulation. There are several obstacles to the use of ketamine for chronic pain. These include low oral bioavailability, a lack of any easily available formulation for chronic delivery, concerns over psychomimetic side effects, and mixed efficacy in clinical trials (61,62).

Adrenergic Agents

Background and Rationale

Autonomic nervous system dysfunction frequently accompanies chronic pain. Although CRPS is the most well-known pain disorder associated with sympathetic nervous system pathology, there are many other conditions whereby the interruption of sympathetic pathways may alleviate symptoms, including central and peripheral neuropathic pain, orofacial pain, fibromyalgia, cancer, pancreatitis, and phantom pain (63-69). Collectively, painful conditions that respond to attenuation of sympathetic nervous system activity are termed sympathetically maintained pain (SMP). There are several mechanisms by which derangements in the sympathetic nervous system can act to induce, maintain, or worsen chronic pain. These include enhanced sensitivity of injured sensory nerves to circulating and endogenously released catecholamines (70,71), increased expression of α–1 adrenoreceptors on primary afferent nociceptors (72,73), hyperalgesic skin of complex regional pain syndrome patients (74), central sensitization rendering A-β-mechanoreceptors algogenic (75), and enhanced discharge and sympathetic sprouting in the dorsal root ganglia (76,77). In some patients with CRPS, a reduction in sympathetic activity has been found (78) with the use of phentolamine, an α-adrenergic antagonist, suggesting that it can be used for sympathetic blockage as a means of analgesia in CRPS.

Clinical Use

Neuropathic Pain

There are limited studies investigating the efficacy of IV infusion of phentolamine for the treatment chronic pain. Many studies have studied have predominantly focused on the utility of IV phentolamine for the diagnosis of sympathetic mediated pain (SMP). Galer (79), in a randomized trial, studied the efficacy of IV infusion of phentolamine in 37 consecutive patients with neuropathic pain. Thirty-seven patients were treated with IV infusion of phentolamine 35 mg over 30 minutes, with 16 of those patients then also treated with 50 mg or 75 mg of IV phentolamine. The results from 45 infusions were recorded with outcomes measured by a pain relief scale completed by patients for 7 days post infusion. Sixteen patients experienced pain relief after treatment and 27 infusions resulted in pain relief. Peak pain relief was delayed in 25 of 27 with reported positive effect from treatment; 7 patients experienced the onset of peak response the night immediately following an infusion, 13 the next day, 3 two days later, and one each 4 and 5 days after infusion (79). The authors reported that all 16 patients who reported pain relief following treatment experienced at least 2 days of relief with each infusion. Eight patients experienced at least one week of pain relief. There was no reported difference in pain relief scores with higher-dosage infusions of IV phentolamine (79).

Raja et al (80) studied 20 patients with chronic pain and hyperalgesia to mechanical and cooling stimuli and concluded that IV phentolamine infusion (total dose 25 - 35 mg) can relieve pain and hyperalgesia. VAS scores were measured for ongoing pain and stimulus evoked pain (evoked by brushing, pressure, and cooling) measured every 5 minutes before, during, and after treatment, and every hour for several hours in 4 patients with greater than 50% relief of pain. The maximum pain relief was approximately 20 - 30 minutes except in 4 patients whose response ranged from 3 to 10 hours of pain relief (80).

Potential Risks and Side Effects

Phentolamine administration is associated with adverse effects of hypotension and/or tachycardia

and arrhythmias (81,82). Other adverse effects include gastrointestinal distress. In clinical practice, the use of phentolamine infusion is limited, mostly due to the lack of prospective controlled trials.

Dexmedetomidine

Background and Rationale

Dexmedetomidine is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1 H-imidazole monohydrochloride. It has a molecular weight of 236.7. Dexmedetomidine is chemically related to clonidine, but is approximately 8 times more specific for α-2 adrenoceptors with α-2:α-1 selectivity ratio of 1620:1, compared with 200:1 for clonidine, especially for the 2a subtype, which makes dexmedetomidine more effective than clonidine for sedation and analgesia (83). Its effects are dose-dependently reversed by administration of a selective α-2 antagonist, such as atipamezole (84).

Pathophysiology

Dexmedetomidine, a pharmacologically active dextroisomer of medetomidine (the methylated derivative of etomidine), is a selective α2-adrenergic receptor agonist (85-87). It binds to transmembrane G-protein-binding adrenoreceptors in the periphery (α2A-adrenoceptor subtype) and in the brain and spinal cord (α2B- and α2C- adrenoceptor subtypes) (86), with a dose-dependent α2-selectivity that is approximately 7- to 8-fold greater than that of clonidine (87,88). In animals, α2-selectivity was observed following the slow IV infusion of low and medium doses of dexmedetomidine (10 – 300 µg/kg), while both α1- and α2-activity was observed following the slow IV infusion of high doses of dexmedetomidine (> 1,000 µg/kg) or following rapid IV administration (85). Dexmedetomidine also binds to imidazoline receptors, potentially explaining the non-α2-adrenoreceptor-related effects of α2-adrenergic receptor agonists (84).

It has a rapid distribution phase. Its steady state volume of distribution is 118 L and its distribution half-life (t½ α) is 6 minutes in adults over the manufacturer-suggested dose ranges of 0.2 - 0.7 µg/kg/h, an elimination half-life (t½ β) of between 2 and 2.5 hours (89) and a clearance of 39 L/h. In a study of 10 post-surgical patients in an intensive care setting, the mean pharmacokinetics of dexmedetomidine (administered as a loading dose of approximately 0.4 µg/kg infused over 10 minutes followed by a maintenance infusion of 0.7 µg/kg/hour) did not differ from those historically observed in healthy volunteers, with the exception of the steady-state volume of distribution (Vss) (90).

Dexmedetomidine undergoes almost complete biotransformation; very little is excreted unchanged in the feces and urine (85). The biotransformation of dexmedetomidine involves cytochrome P450 (CYP)-mediated metabolism and direct glucuronidation. The major metabolic pathways include direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) to 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine; and N-methylation to 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronide (85).

There are no known active or toxic metabolites. However, hepatic clearance may be decreased by as much as 50% of normal with severe liver disease. No differences have been seen between healthy patients and those with renal impairment. The metabolites are eliminated to the extent of 95% in the urine and 4% in the feces. The utilization of dexmedetomidine has been associated with serious episodes of bradycardia, hypotension, sinus arrest, and transient hypertension (section 5){?} (85).

The major site of analgesic action of α2 adrenoceptor agonists is uncertain; however, dexmedetomidine appears to exert analgesic effects at the spinal cord level and at supraspinal sites. Dexmedetomidine may also provide antinociception through non-spinal mechanisms; intra-articular administration during knee surgery improves postoperative analgesia, with less sedation than the IV route (90). Suggested mechanisms are activation of α2A receptors (91), inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of enkephalin.

Dexmedetomidine appears to have analgesic properties in the short-term (92-94). Blaudszun and colleagues (95) performed a systemic review and meta-analysis of randomized controlled trials of perioperative systematic α2 agonists on postoperative morphine consumption and pain intensity. They found that perioperative systemic α2 agonists decrease postoperative opioid consumption, pain intensity, and nausea. Common adverse effects are bradycardia and arterial hypotension. The impact of α2 agonists on chronic pain or hyperalgesia remains unclear because valid data are lacking (95).

It remains unclear whether dexmedetomidine may be effective for providing analgesia in certain chronic

pain states; however, basic research in animal models (96) suggests that it might be conceivable in the future that dexmedetomidine may be a reasonable therapeutic option to utilize along with opioids in efforts to enhance analgesia opioid-induced adverse effects and combat opioid-induced hyperalgesia (OIH). Zheng et al (96) provide some support that these effects against OIH may be due to the ability of dexmedetomidine to modulate spinal cord NMDA-R activation via suppression of NR2B phosphorylation.

Clinical Use

CRPS

Dexmedetomidine has been evaluated in many clinical settings, primarily acute pain states. Clinical studies investigating its efficacy in chronic pain conditions are limited. Nama et al (97) reported a case of a 47-year-old woman admitted with CRPS-I and associated symptoms of severe pain and allodynia refractory to conventional therapy. The patient was treated with sub-anesthetic IV infusion of ketamine (100 µg/kg/h) with adjunct dexmedetomidine (8 µg, one time bolus) for 19 hours and subsequently discharged within 24 hours with complete resolution of her pain and associated symptoms (97). Hall et al (98), in a randomized, double-blind study, examined the effects of dexmedetomidine on analgesia in 7 young healthy volunteers. In 3 sessions separated by a week, a 10-minute initial dose of 6 µg/kg/h dexmedetomidine or saline (placebo) was administered, followed by a 50-minute infusion of 0.2 or 0.6 µg/kg/h dexmedetomidine or saline. Measurements and testing were repeated at the end of infusion and at one and 4 hours post-infusion. A cold pressor test (CPT), which consisted of immersion of the subject's hand into ice water for one minute was performed in study subjects with hemodynamic measurements recorded at the end of the one-minute period (from 45 to 60 seconds). The subjects assessed their pain immediately after the cold exposure via VAS. The authors demonstrated that pain as measured by VAS decreased significantly in both dexmedetomidine groups during the CPT at the 60-min infusion (approximately 30% lower than baseline) with some analgesia remaining up to the first hour of recovery (approximately 15% lower than baseline) (98). Further studies are needed to investigate the efficacy of dexmedetomidine in treating chronic pain conditions.

Potential Risks and Side Effects

The notable potential risks and adverse effects include hypotension, bradycardia, respiratory depression, nausea, and xerostomia.

Bisphosphonates

Background and Rationale

Bisphosphonates are pyrophosphate analogs, traditionally used in the treatment of pathologic conditions associated with abnormal bone metabolism, such as osteoporosis, Paget's disease, and cancer-related bone pain. More recently, results of clinical trials have indicated the potential role of bisphosphonates in the treatment of CRPS (99).

Pathophysiology

Neuropathic bone pain is the result of a combination of factors (99). Periosteum and bone marrow are highly innervated, with peptidergic sensory fibers as well as sympathethic fibers. Low pH, local production of nerve growth factor (NGF), and releases of inflammatory cytokines and prostaglandins activate nociceptive nerve fibers in bone. NGF induces hyperalgesia by upregulation of gene transcription for pain receptors. Osteoclast activation leads to an acidic microenvironment; furthermore osteoclasts, osteoblasts, and bone marrow stromal cells are known to synthesize NGF. It can thus be postulated that inhibition of osteoclasts and other cells that play a role in decreasing pH or producing NGF may reduce or prevent bone pain.

Bisphosphonates exert biological effects through osteoclasts and their precursors, as well as related cells such as macrophages, dendritic cells, and microglia. They suppress bone resorption via osteoclast inhibition and shorten osteoclast life span (99).

Clinical Use

CRPS

Various trials and case studies report the use of bisphosphonate for the treatment of CRPS. A 2009 systematic review by Brunner et al (100) reviewed randomized trials comparing bisphosphonates with placebo with the goal of improving pain, function, and quality of life in patients with CRPS-I with bone loss, and demonstrated in these patients that bisphosphonates have the potential to reduce pain associated with bone loss. All trials show efficacy and patients experienced clinically significant improvement in their symptoms with minimal adverse effects. Most studies showed improvement in pain symptoms and

increased functionality both in the immediate period (100). However sample sizes for most of these trials were small and more data are needed to make further recommendations regarding bisphosphonate use for the treatment of CRPS.

Maillefert et al (101) reported on 7 of 11 patients with CRPS, who experienced clinically significant improvement from IV infusion of pamidronate therapy (30 mg over 4 hours daily for 3 days) in an open prospective study. In this study, the same observer assessed the patients at baseline and after one and 3 months. This evaluation included a VAS and a physician global assessment based on objective signs on clinical evaluation (hyperhidrosis, vasomotor changes, and joint stiffness). The mean VAS decreased from 58.8/100 before therapy, to 41.1/100 at one month ($P < 0.05$; Wilcoxon paired test) and 33.8/100 at 3 months ($P < 0.01$) (101).

In another open prospective study investigating the effects of IV infusion of pamidronate on 23 patients with CRPS, Cortet et al (102) showed significant pain reduction and physical functional improvement. Intravenous pamidronate was infused at a dose of 1 mg/kg/day over 3 hours for 3 consecutive days in 14 cases, 2 consecutive days in 7 cases, and only one day in the last 2 cases. All the patients were unable to receive the pamidronate throughout the 3 consecutive days due to adverse effects. The authors of this study assessed the efficacy of treatment by a decrease of pain VAS, verbal scale (PVS), and the patient and the observer estimated the efficacy of the treatment based on a verbal scale (EVS), all measured before treatment, and 7, 30, 60, and 90 days later. A significant decrease of VAS and PVS were observed between day 0 and day 30 ($P = 0.0002$ and $P = 0.0002$, respectively), day 0 and day 60 ($P = 0.0004$, $P = 0.0004$, respectively), and day 0 and day 90 ($P = 0.00003$, $P = 0.0001$, respectively) (102). A significant increase of EVS was only observed between day 0 and day 90 ($P = 0.03$) (102).

Kubalek et al (103) treated 29 patients with CRPS/RSD. Twenty-five of the patients experienced excellent pain relief from IV pamidronate at a dose of 60 mg/day over 4 hours for 3 consecutive days. Patients were evaluated at 15 and 45 days after pamidronate treatment, with effective treatment defined as a complete disappearance of pain (stopping of analgesics). Functional improvement was rated as favorable if the increase in range of movement was more than 20° compared with the range of movement prior to treatment. On day 15 after the beginning of the treatment, total pain disappearance was obtained in 17 patients (58.6%) and functional improvement was observed in 9 cases (45% of 20) (103). On the 45th day after the beginning of the treatment, total disappearance of pain was obtained in 25 patients (86.2%) and functional improvement was obtained in 14 out of 20 patients (70%) (103).

Breuer et al (104), in another open-label trial (n = 10), administered IV ibandronate, 6 mg infused over 2 hours to CRPS patients over 3 consecutive days and assessed treatment results at 4 weeks post-infusion. The authors reported significant improvement in average and worst pain ratings; the neuropathic pain qualities of "unpleasant," "sensitive," "deep," "intense," "surface," "hot," "cold," "sharp," and "dull"; and hyperalgesia and allodynia.

Robinson et al (105) examined the efficacy of IV pamidronate infusion (single infusion of 60 mg) in a double-blind, placebo-controlled study of 27 patients with CRPS. Patients' pain scores were measured via VAS, global assessment of disease severity scores, and functional assessment (SF-36) scores were documented at baseline and at one and 3 months. The active treatment group (n = 14) reported significant improvement in pain and physical function at 3 months after pamidronate infusion (105). However, at one month there was no significant difference in pain score or in global assessment of disease between the pamidronate and placebo (normal saline) groups.

Varenna et al (106), in a recent, multi-centre, randomized, double-blind placebo-controlled trial, investigated the efficacy of IV infusion of neridronate (100 mg in 2 hours, given 4 times over 10 days) in 82 patients with CRPS-I. After 50 days the former placebo patients were given the same open label regimen of neridronate. The authors concluded that 4 infusions of IV neridronate are associated with clinically relevant and persistent benefits. Treated patients were assessed before randomization, before infusion, at end of treatment, and 10, 20, and 40 days after infusion with the following measures assessed (i) changes in joint volume or local edema, (ii) pain evoked by passive motion, (iii) allodynia and hyperalgesia, (iv) MPQ and SF-36 questionnaire to asses functional status, and (v) a count of the number of NSAID or acetaminophen tablets taken weekly. Significant decreases across all measures were seen compared to placebo at the conclusion of the study (106). IV bisphosphonate infusion therapy was also reported to be beneficial in treating CRPS in an earlier double-blind, randomized, placebo-controlled study by Varenna et al (107), in which 32

patients with CRPS were treated with IV clodronate (300 mg) or placebo infusion for 10 consecutive days.

Potential Risks and Side Effects

Bisphosphonates are usually well tolerated. The side effects are transient and tolerable (99). Common side effects include flu-like symptoms or acute phase reaction during the first 3 days following infusion. These symptoms tend to respond to anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs. A subgroup of patients on chronic IV bisphosphonate treatment for multiple myeloma or bone metastases from other primary malignancies has been reported to have osteonecrosis of the jaw. Overall, bisphosphonates have a positive outlook regarding their future clinical use, specifically as an effective treatment modality for CRPS.

Conclusion

This article is intended to provide an overview of the current literature on the management of chronic pain with commonly used intravenous infusions.

Given the available clinical evidence, this review indicates that the aforementioned infusions may have a limited overall clinical utility in selected patients. Lidocaine and ketamine are the most studied amongst the agents cited in this review. Their therapeutic and side effects have also been investigated extensively in prospective randomized controlled trials.

Phentolamine, dexmedetomidine, bisphosphonates, and a few other rarer compounds, not reviewed in this article, still require significant research.

Further investigation is needed to evaluate clinical significance of infusion therapy.

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