Case Report: Limbic System Activation by Intravenous Lidocaine in a Patient with a Complex Regional Pain Syndrome and Major Depression

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ABSTRACT

Intravenous lidocaine is used to treat various neuropathic pain states. Systemic local anesthetics have been reported to cause behavioral alteration via limbic system activation. This case report describes a dramatic behavioral change in a patient receiving intravenous lidocaine and suggests a possible use of lidocaine to discriminate somatic and affective pain characteristics.

Key Words: Lidocaine; Chronic Pain; Mood Disorder; Limbic System

Introduction

Intravenous lidocaine, a membrane stabilizing medication, decreases spontaneous neuronal firing, and has been shown to be beneficial in the treatment of neuropathic pain states such as complex regional pain syndromes [1,2,5]. Lidocaine has also been shown to be a predictor of the efficacy of mexiletine in the treatment of arrhythmias and in the treatment of neuropathic pain [3,4].

Infusion of lidocaine and other local anesthetics has been associated with mood changes, severe anxiety, and psychotic reactions. This case describes acute onset of severe agitation and apparent flashbacks following an intravenous lidocaine infusion in a patient with complex regional pain syndrome type I, or reflex sympathetic dystrophy, due to a work-related burn injury to his left leg and severe untreated major depression.

Case Report

A 44-year-old man presented to the Stanford Pain Management Service for treatment of a complex regional pain syndrome type 1 of his left lower extremity. This work-related injury was caused by a burn injury approximately 6 months prior to our treatment. Prior treatments included weak opiates such as hydrocodone/acetaminophen, amitriptyline (low doses), and tramadol. His past medical history, beyond his injury and current chronic pain, was unremarkable. There was no history of chronic changing patterns of pain, nor a history of drug or alcohol dependence or abuse. On previous examinations, the patient had allodynia of the medial aspect of his left leg. He also had hyperesthesia of the dorsal and plantar aspect of his left foot. An intravenous lidocaine trial was scheduled to assess the therapeutic value of membrane stabilizing agents for this patient’s neuropathic pain condition.

The patient’s psychiatric history was unremarkable prior to his injury. There was no evidence of depression, significant anxiety, prior life-threatening events or related sequelae, no history of antisocial behaviors or other suggestions of premorbid character pathology. In the months after his accident, the patient noted severe fatigue, decreased appetite, poor concentration, feelings of worthlessness, hopelessness, and a severely depressed mood. He also reported waxing and waning suicidal ideation with a plan to run his truck into a wall or off a
cliff. He had not followed through with these plans because he felt a responsibility to be present when his granddaughter was born. He had not sought treatment for his depression and had not been offered treatment.

At the Stanford Pain Management Center, a computer-controlled Harvard 200 infusion pump is used to provide a stable plasma concentration of lidocaine. This infusion system allows a more thorough evaluation of the relationship between plasma concentration and the patient’s reporting of subjective changes in pain characteristics [6,7,8]. Further, we use a visual analog scale (VAS) to rate pain response rather than testing for changes in tactile allodynia.

The patient received a lidocaine infusion with step-wise dose increases of the blood lidocaine concentration from 3 μg/mL to 5.5 μg/mL escalating over a period of 30 minutes. The trial was discontinued after the patient demonstrated several behavioral changes. The patient became acutely agitated, attempted to get off the gurney, and began to yell incoherently. His wife was brought into the clinic to calm him down. She also reported a recent history of similar experiences occurring at night (‘nightmares’), though none had been this severe.

The patient was given midazolam 4 mg titrated to sedation. The patient was tachycardic; however, there were no signs of hypoxia or blood pressure changes. There were no tonic or clonic movements, oral or manual automatisms, or other evidence of seizure-like activity. Although he was sedated for 30 minutes, he continued to have a behavioral disturbance. He was escorted to the emergency department (ED) for an evaluation by the psychiatry service.

In the ED, the patient continued to be agitated and was placed in 4-point restraints by security personnel. He was thrashing in 4-points for nearly 30 additional minutes. No mention of the patient’s orientation was noted during this period of agitation, nor whether he could follow commands. His vital signs on admission to the ED were 130/80 mm Hg, pulse 150 bpm, respirations 20 per minute, temperature of 35.6°C. He apparently was able to respond to questions concerning review of systems by the ED.

A psychiatrist evaluated the patient 30 minutes after arrival to the ED. The patient was alert and oriented to person, place, and time. His affect was described as flat and his mood was depressed. He denied suicidal or homicidal ideation, or symptoms consistent with psychosis. The patient met diagnostic criteria for major depression but declined psychotherapy or antidepressants and was discharged home.

Discussion

Lidocaine and other local anesthetics have been known to have multiple side effects on the central nervous system and cardiovascular system [9]. The toxicity is dose related to plasma concentration (μg/mL). Systemic reactions initially involve CNS activation with the patient describing dizziness, tinnitus, and audio-visual disturbances (approximately 5 μg/mL). At increasing doses, muscle twitching, tremors, facial numbness, and even generalized convulsions with tonic-clonic movements may develop until CNS depression or coma is reached (10 μg/mL). At higher blood levels, respiratory and cardiovascular depression will occur (15 μg/mL).

The usual side effects considered with lidocaine infusion trials include tinnitus, perioral numbness, dizziness, and drowsiness. Using our Stanford protocol, the lidocaine concentration was increased to 5.5 μg/mL, which is associated with many of these side effects. Seizure activity, however, typically occurs at higher blood levels (10 μg/mL).

Case reports have described psychiatric symptoms following lidocaine as doom anxiety and other mood changes [10,11]. Procaine, another local anesthetic similar to lidocaine, has also been associated with doom anxiety and dysphoric reactions. Studies of the CNS effect of procaine infusions in normal subjects reveal a selective activation of the anterior amygdalocentric limbic system. Specifically, the amygdala (bilaterally or unilaterally), the anterior cingulate and adjacent cortical areas are activated. Selective pharmacologic activation of limbic system structures with procaine produced changes in emotional and psycho sensory experience. Activation of the visual cortex was associated with visual hallucinations. Psycho sensory experiences included auditory and visual hallucinations, fear, and euphoria.

Lidocaine and other local anesthetics have been shown to produce acute psychotic reactions [12]. The features of these reactions resemble a limbic disorder, specifically limbic kindling. Some of the clinical observations in patients include marked de-personalization and intense heat, similar to the observations of the patient discussed above. Lidocaine selectively activates the limbic system and may produce behavioral complications due to the anxiety and hallucinations observed in temporal limbic epilepsy. Some authors suggest that anticonvulsants, particularly benzodiazepines, should be used to prevent lidocaine toxicity and behavioral sequelae.
Intravenous lidocaine has been used extensively to treat various neuropathic pain conditions. Similar to other referral centers for pain treatment, many patients with chronic pain treated at Stanford have concurrent psychiatric conditions such as depression and posttraumatic stress disorder (PTSD). The patient described in this case report meets criteria for major depression, and may have had PTSD, given his wife’s report of the nightmares, which resembled the lidocaine-induced state. However, as the patient was somewhat guarded, to the point of refusing treatment of his depression, other symptoms consistent with PTSD were not elicited.

The reaction to lidocaine did not appear to represent delirium, though orientation was not tested during the acutely agitated state. Typically, sedation and delirium are uncommon after an intravenous lidocaine infusion, since the local anesthetic is metabolized so quickly. A partial seizure and postictal state could have been evident with this patient, although no specific seizure motor activity was noted. The well-oriented state and lack of any postictal confusion following this episode weighs against the involvement of seizure-like activity.

A lidocaine infusion trial is used to predict whether the patient will respond to oral sodium-channel blockade agents for the treatment of neuropathic pain. Lidocaine infusions have also been used to treat nonspecific pain conditions such as postoperative pain, myalgias, and burn injuries [14]. In our clinical experience, many patients with acute pain report considerable benefit from lidocaine infusions. In our population of patients with chronic pain, the benefit ratio is not as high. Indeed, some patients, like the one described above, have behavioral disturbances or even a worsening of their chronic pain.

Recently, a new concept of a limbically augmented pain syndrome (LAPS) was reported [15]. This model tries to clarify the mind-body connection of chronic pain using neuropsychological principles of affective and somatosensory pain. Cortico-limbic sensitization may be the reason why certain patients with chronic pain respond positively to lidocaine. Those patients with a predominant somatosensory neuropathic pain syndrome may benefit from intravenous lidocaine’s suppression of spontaneous ectopic neural activity. Other patients with a predominant affective component or limbically augmented pain syndrome may not respond to lidocaine or even develop behavioral disturbances.

Clinically, intravenous lidocaine seems to produce a more profound effect in treating neuropathic pain than other membrane stabilizing oral agents. Lidocaine is used as a predictor of efficacy of these oral agents, although the correlation is not identical. Perhaps intravenous lidocaine is more effective as an analgesic because of the systemic local anesthetic effect on limbic system structures that are linked with pain perception. Those patients with a lower affective component of pain may derive benefit from a lidocaine infusion suppressing limbic activity at low plasma levels (3–5 μg/mL), similar to suppressing spontaneous neural activity. Other patients with affective disorders may be limbically sensitized. Lidocaine may induce psychological sensations such as fear and anxiety, subsequently worsening the patient’s pain experience. This result may occur despite plasma concentrations lower than neurophysiologic toxic levels for seizure activity.

Clearly further studies are needed to elucidate this theory. Novel neuroimaging technology, such as functional magnetic resonance imaging, may be useful to study neuroactivation of patients with chronic pain receiving intravenous lidocaine when compared to subjects without any pain syndromes [16,17]. Intravenous lidocaine may provide a test for identifying patients with a predominant affective component of pain compared with those with a predominant somato-sensory pain component. However, further studies of the differential effects of lidocaine in well-defined, homogeneous samples of patients with chronic neuropathic pain, with and without affective disorder, are needed to test this hypothesis.

References
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