Systemic Naloxone Infusion May Trigger Spasticity in Patients With Spinal Cord Injury: Case Series

Nancy L. Brackett, PhD, HCLD^{1,2}; Emad Ibrahim, MD^{1,2}; Andrei Krassioukov, MD, PhD³; Charles M. Lynne, MD^{1,2}

¹The Miami Project to Cure Paralysis, Miami, Florida ²University of Miami Miller School of Medicine, Miami, Florida

³ICORD, School of Rehabilitation, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

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Abstract

Background/Objective: Three patients with spinal cord injury (SCI) and 3 able-bodied (AB) patients were infused with naloxone during a study to examine their neuroendocrine function. An unanticipated side effect occurred during the naloxone infusion. All 3 patients with SCI, but none of the AB patients, experienced profoundly increased spasticity during the naloxone infusion. Our report describes this side effect, which has potential implications for the clinical treatment or scientific evaluation of individuals with SCI.

Methods: All patients were in good general health and medication free for 11 days or longer before the study. Each patient was placed on a 30-hour protocol to analyze pulsatile release of gonadotropins. Physiologic saline was intravenously infused on day 1 to serve as a control period for naloxone infusion on day 2.

Results: AB patients experienced no muscle spasm activity or any other side effects at any time during the study. In contrast, all 3 patients with SCI experienced a profoundly increased frequency and duration of spasticity in muscles innervated by the nerve roots caudal to their level of injury. In all 3 patients with SCI, spasticity increased only during the period of naloxone infusion. Within 1 hour of stopping naloxone, spasticity returned to baseline levels.

Conclusions: Naloxone infusion produced a differential effect on the muscle activity of men with SCI compared to AB men with intact spinal circuits. Consistent with previous studies, the results of this study indicate a relationship between opioid neuromodulation and spasticity after SCI.

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Key Words: Naloxone; Endorphins; Opioid; Spasticity; Spinal cord injuries

INTRODUCTION

This report describes an unanticipated side effect that occurred during naloxone infusion of men with spinal cord injury (SCI). As background, 3 men with SCI and 3 able-bodied (AB) men participated in a study to evaluate their neuroendocrine function. The study protocol included an intravenous (IV) infusion of naloxone to antagonize gonadotropin release (1–5). During the

naloxone infusion, a side effect occurred in the patients with SCI, but not in the AB patients. The patients with SCI experienced profoundly increased spasticity during the naloxone infusion compared with their self-reported baseline state. This side effect was unexpected and previously unreported in the literature. We believe this finding has implications for the clinical treatment and/or scientific evaluation of patients with SCI.

METHODS

All patients had a medical history and physical examination before participation in the study. The level of injury, age, and years after injury of the 3 patients with SCI were, respectively as follows—patient 1: level of injury (LOI), T6; 33 years old; 11 years after injury; patient 2: LOI, C4; 30 years old; 5 years after injury; patient 3: LOI, C4; 42 years old; 26 years after injury. The ages of the 3 AB

Please address correspondence to Nancy L. Brackett, PhD, HCLD, The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Lois Pope Life Center, Room 1-27, 1095 NW 14th Terrace, Miami, FL 33136; phone: 305.243.1239; fax: 305.243.3913 (e-mail: NBrackett@miami.edu).

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patients were 22, 23, and 37 years old. All patients were in good general health and had no history of recent alcohol or substance abuse. All patients were free from all medications for at least 11 days before the study.

Each patient was placed on a protocol to analyze his pulsatile release of gonadotropins (luteinizing hormone and follicle-stimulating hormone). For this protocol, patients were admitted to the General Clinical Research Center of a major medical center. Patients arrived the night before treatment onset for an adaptation period. The next morning, an intravenous catheter with a heparin lock was inserted in the arm of each patient, and 3 mL of blood was drawn every 15 minutes for a period of 30 consecutive hours. Cardiovascular parameters and other vital signs were monitored. Physiologic saline was infused from 10:00 AM to 4:00 PM of day 1 to serve as a control period for the infusion of naloxone during the same hours of day 2. Physiologic saline was administered as an IV bolus of 8 mL administered over 1 minute, followed by an IV drip of 10 mL/h for 6 hours. Naloxone hydrochloride (Narcan, DuPont Pharmaceuticals, Wilmington, DE) was administered as an IV bolus of 8 mg in 8 mL physiologic saline dispensed over 30 minutes followed by an IV drip of 24 mg in 60 mL physiologic saline dispensed at the rate of 10 mL/h for 6 h (4 mg/h). This dose of naloxone was administered to antagonize the opioid modulation of gonadotropin release (2).

RESULTS

Cardiovascular parameters and all vital signs were stable in both groups of patients during all stages of the study. AB patients experienced no muscle spasm activity or any other side effects at any time during the study. In contrast, each patient with SCI experienced a profoundly increased frequency and duration of spasticity in muscles innervated by the nerve roots caudal to his level of injury. In all 3 patients with SCI, spasticity increased only during the period of naloxone infusion. Patients 1 and 2 with SCI experienced increased spasticity within 5 minutes, and patient 3 experienced increased spasticity within 30 minutes after delivery of the naloxone bolus.

The increased spasticity continued throughout the entire 6-hour naloxone infusion period. During this time, spasms could be triggered very easily, for example, by very slight changes in posture or by very slight cutaneous stimuli (ie, bed sheet brushing against leg). In addition, the patients with SCI experienced the presence of spontaneous spasms (no apparent stimuli). Within 1 hour of stopping the naloxone infusion, each subject's muscle spasm activity returned to baseline levels. No increased spasticity occurred at any other time during any other treatment period. No sequelae of this activity or subsequent recurrence were noted. There were no changes in pulse, blood pressure, or respiratory measurements in the patients with SCI during the naloxone infusion.

DISCUSSION

Spasticity is a common complication of SCI, resulting from hyperexcitability of stretch reflexes. Muscle spasms and increased tone may disturb sitting balance, interfere with self-care activities, endanger transfers, and significantly affect quality of life of those individuals (6). Control of spasticity is among the major goals of management of individuals with SCI. Baclofen [4-amino-3-(4-chlorophenyl)-butanoic acid] is commonly considered the treatment of choice for control of spasticity after SCI (7), among other commonly prescribed oral and intrathecal medications. However, there are also studies suggesting that intrathecal administration of morphine also may be useful in treatment of spasticity after SCI (8,9).

A primary site of action of spinal epidural or intrathecal morphine is in the neuronal circuits within the dorsal horn (10). Morphine by systemic or spinal administration is receptor specific and affects primarily the polysynaptic reflexes associated with stimulation of A delta or C fibers, with little or no effect on the monosynaptic segmental reflexes (10,11). Therefore, morphine could not only block afferent pain transmission but also the reflex arc that contributes to development of spasticity (10). It has been suggested that the analgesic effect of spinally administered lipid-soluble opioids is caused in part by uptake into plasma and distribution to brainstem opioid receptors (12).

Most patients with SCI experience a baseline level of spontaneous and intermittent muscle spasm activity (spastic hypertonia and hyperreflexia) below their level of injury. In our study, this baseline level was profoundly increased during naloxone infusion in 3 of 3 patients with SCI. Naloxone hydrochloride is a pure narcotic antagonist (ie, it does not possess agonistic properties), which antagonizes the effects of opioids by competing for the same receptor sites (13). The dose of naloxone used in our study was high (4.0–8.0 mg) compared with the dose typically administered for reversal of narcotic overdose (0.4–2.0 mg). This high dose was required to antagonize the opioid modulation of gonadotropin release (2,4). However, even with this high dose of naloxone, control subjects were asymptomatic throughout the treatment period.

These findings indicate a relationship between opioid receptors and spasticity, as previously suggested (8,9). As summarized in a review by Pappalardo et al (14), the pathophysiology of spasticity has not been completely clarified. Historically, it has been attributed to an interruption of the neural network controlling the muscle stretch reflex in the central nervous system, with hyperexcitability and exaggeration of tendon jerks (15). There are many excitatory and inhibitory synaptic circuits influencing the alpha and gamma motor neurons and the final common motor pathway. Inhibitory mechanisms include descending reticular pathways, nonreciprocal Ib inhibition, presynaptic inhibition of the Ia circuitry,

recurrent inhibition through Renshaw circuitry, and reciprocal Ia inhibition (14).

Spasticity is associated with sprouting of descending motor pathways controlling alpha and gamma motor neurons, and new synaptic connections are formed with spinal neurons. An imbalance between these control systems can lead to hyperexcitability of the stretch reflex arc with alpha and gamma motor neuron hyperactivity, followed by an increase of muscle tone (14). In spastic paraplegia, excitatory tonic activity in spinal motor neurons may result from a decrease in inhibition mediated by inhibitory interneurons (16).

Between C4 and T2 of the dorsal horn of the rat, spinal cord mu receptors have the highest binding, followed by delta and then kappa receptors (17). High levels are also found in the substantia gelatinosa in the vicinity of small primary afferent terminals (18). In the thoracic cord, significant levels of opioid binding are observed in the intermediolateral cell column where the preganglionic sympathetic neurons are found (19). Physiologic studies have shown that opiates can exert significant receptor-selective effects on spinal motor neurons. These effects are stereospecific and antagonized by naloxone (20).

The presence of opioid receptors throughout the spinal cord provide further evidence for the effect of morphine on spasticity (20). When spinal mu opioid receptors are blocked, subsequent systemic administration of mu opioids fails to produce an analgesic effect (21). In the intact spinal cord, opioids regulate antinociception, affective behaviors, addiction, gastrointestinal motility, blood pressure, stress responses, central control of endocrine functions, locomotion, thermoregulation, and processing of sensory information (22–24).

Normal motor function is not affected by intrathecal or epidural morphine at either maximum analgesic doses in humans (25) or up to several times that concentration in animals (26,27). However, where abnormal motor tone is present (as in spasticity after SCI or in multiple sclerosis), opiates (morphine and fentanyl) will produce evident relaxation (8,9). This phenomenon is achieved at a dose that, in humans, is commonly associated with an opioid receptor interaction (1–2 mg) and is reversed by naloxone.

Systemic morphine inhibits ascending dorsal horn neurons through stimulation of spinal mu opioid receptors (28). The locomotor rhythm evoked by perineal stimulation in clonidine-treated spinal cats can be produced more easily when naloxone is administered (29). In intact rats, an inhibitory mechanism counteracts the long-lasting increase in excitability of the flexor reflex seen in spinal animals after high-intensity, repetitive stimulation of C-fibers. Morphine increased the excitability of the spinal cord during high-intensity stimulation (30). In paraplegic humans, systemic morphine at analgesic doses will attenuate the polysynaptic reflex of the tibialis anterior muscle evoked by sural nerve

stimulation with no effect on the monosynaptic H reflex (31,32). Our results are consistent with the above reports.

CONCLUSION

In summary, we report that a high dose of naloxone (4–8 mg) produced a differential effect on the muscle activity of men with SCI compared with AB men with intact spinal circuits. Previous studies in animals (20,26) and humans (25) showed that, through inhibition of intraspinal polysynaptic reflexes, morphine could ameliorate abnormal muscle tone and spasticity of spinal origin. Increased spasticity after naloxone infusion in this study is consistent with these observations. A high dose of naloxone probably facilitated the segmental reflex pathways and contributed to the increased tone in subjects with SCI. The results of this study further indicate a relationship between opioid neuromodulation and spasticity after SCI.

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