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Local Anesthetics as Pain Therapy in Horses

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KEYWORDS

• Lidocaine • Anesthesia • Antinociception • Horse

Despite the introduction of new drugs and techniques, it is recognized that many human patients experience moderate to severe pain postoperatively. In addition, it is now understood that postoperative pain can result in undesirable sequelae, such as chronic pain.¹ Although anthropomorphizing can lead to erroneous conclusions, it appears reasonable to assume that horses may also develop chronic pain after an episode of acute postoperative pain, and a recent study indicates that acute laminitis may lead to neuropathic pain.² Presently, the arsenal of analgesic drugs for use in the equine patient is limited. Systemic use of opioids is restricted because of adverse effects such as behavioral changes³ and ileus.⁴ The epidural administration of local anesthetics is mainly limited to pain relief of the perineum because of the need to maintain motor function, although morphine can be administered by this route without causing motor block. However, many clinicians see epidural drug administration as invasive and carrying the risk of infection. Consequently, equine practitioners continue to rely heavily on less efficacious drugs, primarily nonsteroidal anti-inflammatory drugs, for pain control. Thus, there is a need for safe and inexpensive alternative pain therapies for horses.

Studies in human patients and laboratory animals have demonstrated that systemically administered local anesthetics, such as lidocaine and its congener mexiletine, can reduce the intensity of postoperative and neuropathic pain, although the mechanisms of lidocaine's actions are uncertain. Mexiletine is rarely used clinically, primarily because it has significant side effects. Recent studies indicate that systemic lidocaine may have potential as an analgesic and as a supplement to general anesthesia in horses.

HISTORICAL PERSPECTIVE ON THE SYSTEMIC USE OF LOCAL ANESTHETICS

The intravenous (IV) administration of the local anesthetic procaine, for analgesic purposes, was initially described by Gordon in 1943,⁵ and further reports on its use

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in human patients followed.^{6,7} Lidocaine (lignocaine) is an amide local anesthetic that is primarily used systemically as an antiarrhythmic drug; however, the use of IV lidocaine for anesthetic and analgesic purposes was first reported over 50 years ago.^{8,9} In 1954, De Clive-Lowe and colleagues¹⁰ described their experiences with the administration of lidocaine in association with succinylcholine for general anesthesia in 1,000 human patients. It was later reported that the incidence of postoperative pain was significantly less in patients that were administered lidocaine perioperatively and, surprisingly, the analgesic effects were still evident on the third postoperative day.¹¹ In spite of those early clinical studies demonstrating the anesthetic and analgesic effects of IV lidocaine, there was no further interest in the topic for over 30 years, presumably due to concerns of toxicity.

REDISCOVERY OF LIDOCAINE'S ANTINOCICEPTIVE EFFECTS

Renewed interest in the systemic administration of local anesthetics began in 1986, when it was demonstrated that intra-abdominal instillation of bupivacaine decreased the duration of postoperative colonic ileus in human patients.¹² This research was soon followed by a study that demonstrated the efficacy of IV lidocaine in decreasing the duration of colonic stasis.¹³ Importantly, these studies showed that local anesthetics were efficacious at blood concentrations less than those considered to be toxic; however, it is important to note that bupivacaine is not administered intravenously because of its narrow therapeutic index.

The systemic administration of lidocaine for neuropathic pain has been the focus of numerous studies,^{14,15} but the efficacy of lidocaine for the treatment of acute postoperative pain has gained attention of late. The analgesic effects of sodium (Na⁺) channel blockers, such as lidocaine and mexiletine, have been demonstrated in studies in rats^{16,17} and human volunteers.^{18,19} In human patients, IV lidocaine decreases postoperative pain,^{18,20} is antihyperalgesic²¹ and anti-inflammatory,²² improves bowel function postoperatively,²³ and facilitates rehabilitation.²⁴

Although it was initially established that IV lidocaine has analgesic effects in patients with chronic neuropathic pain^{14,15} and is efficacious for the treatment of visceral pain,²⁵ the results of its efficacy in postoperative pain were conflicting. It is now understood that differences in study findings are related to the timing of the lidocaine administration, and perhaps the dose of lidocaine administered and the type of noxious stimulus. The intraoperative administration of large doses of lidocaine resulted in analgesia and morphine-sparing effects.^{10,11} Intraoperative administration of lidocaine, followed by a constant infusion for 24 hours postoperatively, resulted in significant analgesia on the first and second postoperative day.²⁶ In contrast to the aforementioned findings, administering a small dose of lidocaine, by infusion, in the postoperative period did not produce analgesic effects.^{27,28}

ORIGINS OF POSTOPERATIVE PAIN

Current understanding of pain mechanisms has progressed from the Cartesian concept that pain resulted from the direct transmission from peripheral receptors and fibers, via the spinal cord, to a pain center in the brain. It is now understood that nociceptive input is transmitted to the spinal cord, or specific cranial nerves, by myelinated A δ and unmyelinated C-fibers. The signal crosses the synaptic junction in the dorsal horn of the spinal cord via a series of chemical interactions before being transmitted by nociceptive-specific or nonspecific wide dynamic range (WDR) neurons.

It is recognized that tissue injury may induce changes in the responsiveness of the nociceptive system by causing peripheral and central sensitization.²⁹ Generally,

postoperative pain is believed to result from the interaction of three sources: (1) trauma at the surgical site, which generates impulses in peripheral neurons; (2) peripheral sensitization of nerve fibers at the surgical site due to the effects of inflammatory mediators; and (3) central sensitization of the spinal cord subsequent to prolonged barrage from nociceptive inputs. Although the trauma of incision and tissue manipulation activates central pathways implicated in sensitization, its influence may be restricted to the intraoperative period.³⁰ It is currently understood that local anesthetics can be used perioperatively to affect all three aforementioned sources of postoperative pain.

Peripheral sensitization involves (1) lowering of the response threshold in primary afferent fibers, (2) an increase in response magnitude to suprathreshold stimuli, (3) an increase in spontaneous activity, and (4) an increase in receptive field size.²⁹ Decrease in tissue pH after surgical incision may also contribute to postoperative pain and hyperalgesia.³¹ In addition, inflammatory mediators and the increased temperature at the surgical site increase the activity of the transient receptor potential vanilloid type 1 (TRPV1) receptor, resulting in the generation of action potentials that may be perceived as pain.³² Neuronal excitability is amplified by chemokines and cytokines, such as tumor necrosis factor α (TNF- α), interleukin (IL)-6, and prostaglandin E₂ (PGE₂), which, together with nerve growth factor, increases the expression or activity of voltage-gated Na⁺ channels (VGSCs).³³

In central sensitization there is a decrease in the pain threshold as a result of exposure to excessive and prolonged nociceptive input altering the responsiveness of the central nervous system (CNS).³⁴ Thus, after development of central sensitization, an innocuous stimulus is perceived as noxious.³⁵ Secondary hyperalgesia, another consequence of central sensitization, is an exaggerated response to stimuli applied to undamaged tissue surrounding the site of injury.³⁶ The process of central sensitization involves a number of neurotransmitters and receptors including the N-methyl-D-aspartate (NMDA) receptor.

The idea that inhalational anesthesia does not protect against central sensitization was proposed by Crile³⁷ in 1913. He claimed that patients who had regional anesthesia of the surgical site, in addition to inhalational anesthesia, experienced a reduction in postoperative pain. This concept of preemptive analgesia was reintroduced in 1983 by Woolf,³⁸ who provided evidence, based on animal studies, to support Crile's observations.

MECHANISMS OF LIDOCAINE-INDUCED ANTINOCICEPTION

The mechanisms by which systemic lidocaine suppresses postoperative pain are uncertain; however, a number of mechanisms have been proposed for its antinociceptive effect (**Box 1**). Local anesthetics were initially considered to block only Na⁺ channels; however, there is an increasing body of evidence that these drugs also modulate a wide range of ion channels, receptors, and nociceptive pathways in the CNS. Interestingly, some of these effects occur at concentrations of local anesthetic much less than those required for Na⁺ channel blockade.²² At clinically relevant blood concentrations of lidocaine, there is little or no effect on impulse conduction in uninjured peripheral nerves. The plasma concentration (2–5 $\mu\text{g/mL}$) of lidocaine that is efficacious in alleviating pain is profoundly less than what is required to block electrically evoked peripheral nerve conduction in nociceptive C and A δ fibers, as this would require plasma concentrations of approximately 250 $\mu\text{g/mL}$.³⁹

Action at Sodium Channels

VGSCs transmit electrical signals along sensory neurons to the CNS by generation of rapid action potentials. VGSCs are transmembrane proteins with gated pores. Opening

Box 1**Reported effects of systemic lidocaine**

Antinociceptive and minimum alveolar concentration-sparing mechanisms

- Blockade of sodium channels
- Blockade of calcium channels
- Blockade of potassium channels
- Blockade of presynaptic muscarinic receptors
- Blockade or activation of transient receptor potential vanilloid type 1 receptors
- Blockade of N-methyl-D-aspartate receptors
- Activation of γ -aminobutyric acid receptors
- Activation of glycine receptors

Anti-inflammatory mechanisms

- Inhibition of sequestration, migration, and activation of polymorphonuclear cells (PMNs).
- Inhibition of PMN adherence to endothelial cells
- Inhibition of $\text{Na}^+ - \text{H}^+$ exchanger in PMNs
- Suppression of histamine release from mast cells
- Inhibition of nuclear factor κB
- Decrease in chemotactic factors and cytokines
- Decrease in albumin extravasation and microvascular permeability
- Inhibition of sensory neurons with resultant decreases in release of substance P
- Decrease in release of proinflammatory lipoxygenase products
- Inhibition of the release of toxic oxygen metabolites
- Decreased expression of inducible nitric oxide synthase

and closing of these pores is controlled by changes in transmembrane voltage gradients.⁴⁰ Lidocaine binds to a receptor site within the α -subunit of the channel, thereby blocking Na^+ conduction and preventing the generation of an action potential.⁴¹

Interaction of lidocaine with sodium channels

Lidocaine is a weak base and is available commercially as a salt. The salt form dissolves in an aqueous solution into the nonionized (lipid soluble) and ionized (hydrophilic) forms. The nonionized form of lidocaine crosses the axonal membrane more readily, becomes protonated (**Fig. 1**), and then attaches to the binding site for local anesthetics, located on the inside of the sodium channel,^{42,43} resulting in blockade of sodium transfer across the channel. The ionization constant (pKa) of lidocaine is 7.9 and, at physiologic pH (7.4), 79% of lidocaine exists in the ionized form.⁴⁴ Thus, if the pH of the solution was closer to the pKa, more of the nonionized form would be present, and the onset of nerve block would be more rapid. Sodium bicarbonate is sometimes added to the lidocaine solution to increase pH and, thereby, decrease the onset time and increase the duration of the nerve block,⁴⁵ in addition to decreasing pain on injection.⁴⁶ However, there is no evidence that the efficacy of systemically administered lidocaine is decreased by the magnitude of pH change that might occur clinically; therefore, concurrent administration of sodium bicarbonate to acidotic animals cannot be recommended for the purpose of increasing the efficacy of lidocaine.

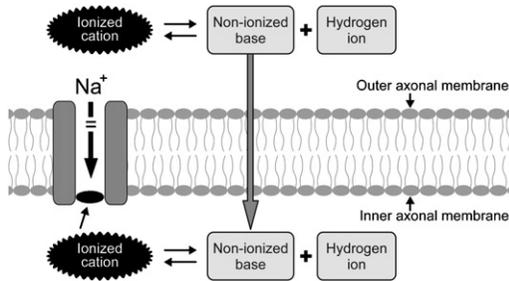


Fig. 1. Mechanism of action of lidocaine for Na^+ channel blockade. The nonionized form of lidocaine crosses the axonal membrane and becomes ionized (protonated). The ionized form binds to the cytoplasmic side of the Na^+ channel, thereby blocking Na^+ transfer across the membrane.

Sodium channel subtypes

There are at least nine different VGSC subtypes in the nervous system and numerous sensory neuronal channels have been implicated in pain mechanisms. The various Na^+ channel subtypes are encoded by different genes and changes in gene expression, resulting in upregulation of channels, may occur following tissue injury.⁴⁷ VGSCs subtypes $\text{Na}_v1.8$ and $\text{Na}_v1.9$ have been identified in nociceptive dorsal root ganglion (DRG) neurons.⁴⁸ The subtype $\text{Na}_v1.7$ is considered to play a crucial role in nociception because humans lacking functional $\text{Na}_v1.7$ channels are insensitive to noxious stimuli⁴⁹ and a $\text{Na}_v1.7$ knockout mouse model has deficits in response to inflammatory stimuli.⁵⁰ Although $\text{Na}_v1.3$ is not normally expressed in adult sensory neurons, its expression is upregulated as a consequence of chronic inflammation or nerve injury.⁵¹

Blockade of ectopic discharges

Under physiologic conditions, primary afferent neuronal inputs, which encode nociceptive information from the periphery to the spinal cord, are generated only after stimulation of peripheral receptors by chemical, heat, mechanical stimuli, or a combination thereof. However, injury to a peripheral nerve can cause a primary afferent input to be generated spontaneously without activation of peripheral receptors. These spontaneous discharges are often referred to as ectopic discharges. Ectopic discharges in injured nerves result primarily from the activation of Na^+ channels,⁵² and studies in numerous animal preparations indicate that the systemic administration of lidocaine, at clinically relevant concentrations, can silence ectopic discharges in injured nerves.^{16,53}

Action at Calcium Channels

Synaptic transmission in the dorsal horn is triggered by calcium (Ca^{++}) channel opening, and Ca^{++} channels can propagate action potentials, as has been demonstrated in heat nociceptive neurons in mammalian skin.⁵⁴ Voltage-gated Ca^{++} channels closely resemble Na^+ channels in structure and, not surprisingly, are blocked by local anesthetics; although a greater concentration of local anesthetic is necessary when compared with that needed for Na^+ channel blockade.⁵⁵

Action at Potassium Channels

Potassium (K^+) channels are expressed in many areas of the nervous system and have a role in neuronal plasticity. In peripheral neurons, K^+ channels contribute to the decay phase of the action potential and have a role in maintaining the resting membrane potential. A specific K^+ channel, $\text{K}_v4.2$, is thought to play a significant role in

transmitting inflammatory pain in peripheral neurons and is important in neuronal plasticity.⁵⁶ Lidocaine blocks voltage-gated and voltage-independent K⁺ channels, although the affinity of lidocaine for these channels is much less than its affinity for Na⁺ channels.⁵⁷

Inhibition of G Protein-Coupled Receptors

Lidocaine is known to inhibit G protein-coupled receptors (GPCRs), which make up a large superfamily of transmembrane proteins that undergo conformational changes after binding extracellular ligands, resulting in regulation of intracellular enzymes.⁵⁸ These receptors respond to a variety of physical and chemical stimuli, neurotransmitters, neuropeptides, hormones, and glycoproteins. Sensory neuron-specific GPCRs are expressed exclusively on nociceptive neurons and are implicated in the modulation of nociception.⁵⁹ Lidocaine interacts with the signaling of GPCRs to modulate K⁺ and Ca⁺⁺ channel function.⁶⁰

Activation of TRPV1 Receptors

The TRPV1 receptor is a nonselective cation channel that is expressed by sensory neurons and in small-diameter DRG neurons, and was initially identified as the receptor for capsaicin.^{61,62} It is now believed that these channels are sensory transducers that participate in the generation and modulation of nociception evoked by chemical, thermal, and mechanical stimuli.

Lidocaine may activate and sensitize TRPV1, and this activation can contribute to the release of neurotransmitters resulting in nociceptive modulation.⁶³ There is also evidence that TRPV1 and transient receptor potential ankyrin-1 receptors are coexpressed in small-diameter noxious sensory neurons (A δ and C-fibers),⁶⁴ and their activation by systemic lidocaine modulates nociception.

Inhibition of NMDA Receptors

Hypersensitivity in either inflammatory or neuropathic pain is predominantly mediated by N-methyl-D-aspartate (NMDA) receptors.^{65,66} At the spinal cord, lidocaine reduces the postsynaptic depolarization mediated by NMDA receptors.^{67,68} Lidocaine's inhibition of activated NMDA receptors *in vitro* is thought to be due to inhibition of protein kinase C (PKC).⁶⁹ In rats, small concentrations of lidocaine inhibited the depolarizations detected in spinal root recordings resulting from the direct chemical activation of NMDA receptors.^{68,70} The wind-up phenomenon that contributes to central sensitization after repeated or intense noxious stimulation is suppressed by lidocaine applied directly to the spinal cord.⁷¹ Systemic administration of lidocaine suppressed neuronal activity, including C-afferent fiber-evoked activity, in rat spinal cord.⁷²

Anti-Inflammatory Effects

The anti-inflammatory effects of local anesthetics are another important mechanism for their antinociceptive actions (see Box. 1). Inflammatory products, such as PGE₂, 5-hydroxytryptamine, and adenosine, augment the excitability of neurons by enhancing inward currents on Na⁺ channels expressed on primary afferent neurons.⁷³ These changes result in peripheral and central sensitization. Interestingly, the effects of lidocaine on inflammatory cells such as polymorphonuclear granulocytes (PMNs) are not caused by Na⁺ channel blockade because Na⁺ channels are not expressed on PMNs.⁷⁴

Although there is ample evidence, from *in vitro* and *in vivo* studies, for the anti-inflammatory properties of lidocaine, the molecular mechanism underlying these anti-inflammatory effects are not well described. Proposed mechanisms include

effects on cyclic adenosine monophosphate, GPCRs, nicotinamide adenine dinucleotide, $\text{Na}^+ - \text{H}^+$ exchanger, and PKC.²² In lipopolysaccharide-stimulated macrophages, lidocaine significantly decreased inducible nitric oxide synthase expression by suppression of nuclear factor κB activation.⁷⁵ In human surgical patients, perioperative lidocaine administration significantly decreased the ex vivo production of IL-1 α and IL-6.⁷⁶

Miscellaneous Effects of Lidocaine

Gamma-aminobutyric acid (GABA) and glycine are the main inhibitory neurotransmitters in the CNS.⁷⁷ There is ample evidence for the modulating effect of lidocaine on glycine signaling. Indeed, it is suggested that lidocaine may exert some of its antinociceptive activity through glycinergic pathways.^{63,78} Intravenous lidocaine activates the strychnine-sensitive glycine receptors in WDR neurons in rats, resulting in inhibition of transmission of noxious and nonnoxious information.⁶³ Excitation of GABAergic/glycinergic inhibitory interneurons, via TRPV1 receptors, after IV administration of lidocaine, may also have a role in suppression of WDR neuronal activities.⁶³

Lidocaine can inhibit substance P binding to neural cells,⁷⁹ neurokinin receptor-mediated postsynaptic depolarizations,⁶⁸ and glutamate-evoked activity in spinal dorsal horn neurons.⁸⁰

ANESTHETIC AND ANTINOCICEPTIVE EFFECTS OF LIDOCAINE IN THE HORSE

Systemically administered lidocaine has recently gained popularity in equine practice for its volatile anesthetic sparing effects, its presumed antinociceptive actions, and for treatment of ileus. However, to date, there are only a few studies of the effects of intravenously administered lidocaine in either anesthetized or conscious horses.

Anesthetic-Sparing Effects of Lidocaine

In an experimental setting, lidocaine decreased the minimum alveolar concentration (MAC) of halothane in ponies.⁸¹ In clinical studies of horses undergoing surgery, lidocaine alone^{82–84} and in combination with ketamine⁸⁵ decreased the required end-tidal concentration of isoflurane. Lidocaine combined with ketamine and morphine decreased the end-tidal concentration of sevoflurane required to maintain a surgical plane of anesthesia in horses.⁸⁶ These findings are consistent with those of a study in which lidocaine caused a dose-dependent decrease in the bispectral index in anesthetized horses.⁸⁷

The mechanism by which lidocaine decreases the volatile anesthetic MAC is uncertain, but is probably not simply due to its antinociceptive properties, and may involve multiple receptor types (see **Box 1**) such as NMDA, GABA_A, acetylcholine, and glycine.⁸⁸ The magnitude of MAC reduction with lidocaine in ponies is dose-dependent.⁸¹ Small doses of lidocaine (eg, 0.05 mg/kg/min) reduce the MAC by about 20%,⁸¹ and this is consistent with findings in clinical studies that used lidocaine at doses no greater than 0.05 mg/kg/min.^{82,83} A greater dose of lidocaine (eg, 0.1 mg/kg/min) reduces the MAC of a volatile anesthetic by at least 35%.⁸¹

In a surgical model, lidocaine (3.0 mg/kg) was administered IV to horses anesthetized with xylazine and ketamine.⁸⁹ In that study, there was no difference between the lidocaine and saline treatments in regards to the number of supplementary injections of xylazine and ketamine needed to maintain a surgical plane of anesthesia. However, the study could not be tightly controlled because the horses were not weighed before anesthesia, thus drug doses had to be estimated. The study did not evaluate the analgesic effect of lidocaine in the postoperative period.

Adverse effects of lidocaine administration were not reported in any of the aforementioned studies; nevertheless, there is evidence that the intraoperative administration of lidocaine may decrease the quality of recovery.⁹⁰ However, in the authors' experience, this effect can be readily overcome by decreasing the plasma concentration of lidocaine at the time of awakening by (1) stopping the infusion before the end of surgery or (2) decreasing the infusion rate over time or (3) delaying the horse's first attempt to stand by inducing sedation.

Antinociceptive Effects of Lidocaine

The effects of intravenously administered lidocaine on electroencephalography (EEG) parameters were investigated in anesthetized ponies.⁹¹ Under halothane anesthesia, ponies were given a loading dose of lidocaine (5.0 mg/kg, [IV]) over 15 minutes and an infusion of 0.1 mg/kg/min. Lidocaine administration abolished measured EEG changes which are indicative of noxious stimulation during castration; based on these findings, the authors concluded that lidocaine is antinociceptive.

In 2005, Robertson and colleagues⁹² investigated the antinociceptive effects of systemically administered lidocaine in response to visceral and somatic stimuli in conscious horses. Somatic antinociception was assessed using a thermal stimulus, by applying a heat source over the withers. Visceral antinociception was evaluated by the response to colorectal and duodenal distension. Lidocaine was administered as a loading dose of 2.0 mg/kg over 20 minutes and a constant rate infusion (CRI) of 0.05 mg/kg/min. The resulting plasma concentrations of lidocaine during delivery of the noxious stimuli ranged from 0.7 to 1.2 µg/mL. Lidocaine treatment did not have a significant effect on the response to colorectal or duodenal distension in the horses of that study, which was surprising, given that lidocaine dose-dependently inhibited cardiovascular responses to colorectal distension in rats.²⁵ Lidocaine treatment significantly increased the thermal threshold, and this was contrary to the findings in studies using human volunteers, where systemic lidocaine has no effect on thermal thresholds.⁹³

Potential Role in Treating Laminitis-Induced Pain

There is a clinical report that intravenously administered lidocaine provided analgesia in horses suffering from chronic laminitis.⁹⁴ A recent study has demonstrated that the histopathological changes in the sensory nerves innervating the forelimb of horses suffering from chronic laminitis were consistent with those reported in previously characterized neuropathic pain states.² Thus, it seems plausible that systemic lidocaine, which has been shown to be effective for the treatment of neuropathic pain,^{14,15} would be beneficial in the treatment of laminitis.

OTHER POTENTIAL BENEFITS OF SYSTEMIC LIDOCAINE

Besides its anesthetic and antinociceptive effects, lidocaine has properties that make its use desirable in the surgical patient, particularly in the horse undergoing abdominal surgery.

Effect on the Incidence of Post-Operative Ileus

A number of studies with human patients have established that the perioperative use of lidocaine reduces the duration of postoperative ileus (POI).^{13,23,95} The effect of intraoperative administration of lidocaine on the incidence and severity of POI has not been investigated widely in horses; however, in one study, the intraoperative administration of lidocaine to surgical colic patients was thought to be associated with a reduction in

the incidence of POI.⁹⁶ In another study of horses undergoing abdominal surgery, the intraoperative administration of lidocaine (0.025 mg/kg/min) combined with CRI of 0.05 mg/kg/min for 24 hours after surgery was considered to have a beneficial effect on intestinal motility.⁹⁷ In a study of horses with POI, the administration of lidocaine postoperatively resulted in shorter hospitalization time.⁹⁴

Effects on Ischemia-Reperfusion Injury

Systemic lidocaine decreases reperfusion injury following ischemia. In a myocardial ischemia model in dogs, lidocaine reduced the size of the myocardial infarct.⁹⁸ In an ischemic jejunal model in horses, pretreatment with lidocaine decreased plasma PGE₂ metabolite concentration and mucosal cyclooxygenase 2 expression, and ameliorated the effect of flunixin meglumine on promoting mucosal neutrophil infiltration.⁹⁹

Effects in Endotoxemic Animals

Lidocaine has been investigated for its therapeutic potential in various models of endotoxemia in laboratory animals. In rabbits, lidocaine attenuated the hypotension and metabolic acidosis consequent to the endotoxin administration.¹⁰⁰ In rats, lidocaine attenuated endotoxin-induced changes in leukocyte adhesion to endothelial cells and preserved endothelial integrity, as demonstrated by a decrease in macromolecular leakage.¹⁰¹

METABOLISM AND ELIMINATION OF LIDOCAINE

Metabolism of lidocaine in the horse produces monoethylglycinexylidide and glycinexylidide, which are the pharmacologically active metabolites⁸¹ that are de-ethylation products of lidocaine also produced in the human liver via the cytochrome P450 superfamily of enzymes. Thus, lidocaine may be considered to undergo metabolism via the cytochrome P450 system in horses. Lidocaine and its metabolites are excreted in the urine. Feary and colleagues¹⁰² compared lidocaine kinetics in conscious horses and horses anesthetized with sevoflurane, and concluded that general anesthesia changes lidocaine kinetics. Plasma lidocaine concentrations were increased at all times in the anesthetized group, and this was attributed to a decrease in the volume of distribution and clearance of lidocaine. Lidocaine clearance is greatly dependent on hepatic blood flow,¹⁰³ and a decrease in hepatic blood flow, such as may occur during sevoflurane anesthesia, will decrease lidocaine clearance. Additionally, anesthetic drugs metabolized by the cytochrome P450 system may compete for binding sites and delay clearance.

CONTRAINDICATIONS TO SYSTEMIC ADMINISTRATION OF LIDOCAINE

Because of lidocaine's effects on inflammation and phagocytic cell function, there has been concern that inhibiting these functions might increase the incidence of bacterial infections. It appears, however, that the residual polymorphonuclear cell function is adequate and the bactericidal effect of PMNs from human patients being administered lidocaine infusions is only slightly decreased.¹⁰⁴ Nevertheless, in a study of rats inoculated with *Staphylococcus aureus*, five of six rats treated with systemic lidocaine died, whereas only one of six rats in the control group died.¹⁰⁵ Thus, it may be prudent to avoid the use of systemic lidocaine in patients with gross bacterial contamination. Paradoxically, lidocaine has anti-bacterial effects; however, these effects occur at concentrations greater than what can be safely achieved with systemic administration.¹⁰⁶

RECOMMENDATIONS FOR THE USE OF SYSTEMIC LIDOCAINE

Intraoperative Administration of Lidocaine

Based on currently available data from horses and other species, intraoperative administration of lidocaine is expected to decrease the volatile anesthetic MAC, postoperative pain, the incidence and severity of postoperative ileus, and inflammation.

In the authors' hospital, lidocaine is used with isoflurane, ketamine, and xylazine as part of a multimodal anesthetic regimen. After sedation with xylazine hydrochloride and induction of anesthesia with ketamine and diazepam, a loading dose of lidocaine (3.0 mg/kg over 15 minutes) is given and a CRI of 0.1 mg/kg/min is administered during the first hour. The CRI is decreased to 0.075 and 0.05 mg/kg/min for the second and third hours, respectively. Concurrently, the end-tidal concentration of isoflurane is maintained at 0.4% to 0.6%, and ketamine (2.5 mg/kg/hr) and xylazine (0.25 mg/kg/hr) are infused. The lidocaine infusion is generally stopped approximately 20 minutes before the end of surgery. To delay time to first movement, horses are sedated with romifidine (0.04 mg/kg) and ketamine (0.3 mg/kg) when placed in the recovery box. Problems that can be attributed to lidocaine administration have not been encountered while using this technique in approximately 2,000 horses.

Lidocaine Administration to Conscious Horses

Systemic lidocaine may be safely used in the conscious horse; however, in this scenario, careful attention must be given to the loading dose and infusion rate. A loading dose of lidocaine (1.3–1.5 mg/kg) is administered over 3 to 5 minutes, and this is followed by a CRI of 0.05 mg/kg/min. Lidocaine can be safely administered at this rate for many hours, and adverse effects, when they occur, are generally due to an unintentional increase in the infusion rate.

SIGNS AND TREATMENT OF LIDOCAINE TOXICITY

Lidocaine toxicity produces a concentration-dependent spectrum of effects (**Fig. 2**) that are manifested primarily at the central nervous and cardiovascular systems, although cardiac signs of toxicity occur at much greater plasma concentrations.⁴⁴

Systems	Progression of clinical signs with increasing plasma concentration
Central Nervous	Eyelid blinking/ Nystagmus
	Muscle twitching
	Ataxia
	Recumbency
	Seizure
	Coma
Cardiovascular	Hypotension/ Bradycardia
	Cardiovascular collapse

Fig. 2. Clinical signs of lidocaine toxicity. The arrow indicates increasing plasma concentrations of lidocaine. These signs may not necessarily occur as a continuum in all horses.

Because of the relatively large volumes of lidocaine required to produce toxicity in an adult horse, toxicity is unlikely to happen under normal circumstances. Treatment of severe lidocaine toxicity may be unrewarding, thus emphasized the importance of vigilance during lidocaine administration.

CNS Toxicity

Signs of CNS toxicity in conscious horses are initially manifested as eyelid blinking, nystagmus, muscle twitching and ataxia, and the horse may assume sternal recumbency.¹⁰⁷ Some horses have signs of visual dysfunction,¹⁰⁷ which is consistent with reported effects of visual impairment with lidocaine toxicity in human patients.⁴⁴ These signs usually resolve fairly quickly once the lidocaine infusion is stopped. However, treatment with a sedative (eg, xylazine, 0.3 mg/kg, IV) or an anticonvulsant (eg, diazepam, 0.05 mg/kg, IV) may be indicated if CNS signs persist beyond a few minutes. In severe overdosing, the aforementioned signs may progress to seizures, unconsciousness, and respiratory arrest. Paradoxically, lidocaine has been shown to suppress seizures at plasma concentrations less than 5.0 $\mu\text{g/mL}$,¹⁰⁸ and has been used successfully for the treatment of status epilepticus in children.¹⁰⁹

Treatment of seizures should begin quickly and, in addition to sedatives and anticonvulsants, general anesthesia may be necessary in some cases to control the seizures. Although a GABA agonist, such as thiopental or propofol, may be the ideal agent to induce anesthesia; ketamine combined with a benzodiazepine is probably satisfactory if the horse is heavily sedated (eg, xylazine 1.0 mg/kg, IV) because ketamine significantly prevented lidocaine-induced generalized tonic-clonic seizures in mice.¹¹⁰ Guaifenesin, a central muscle relaxant, should be beneficial in decreasing the skeletal muscle manifestations of toxicity. Provision of supplemental oxygen is indicated because of the increase in oxygen demands in the brain and muscle; hypoxemia further exacerbates lidocaine toxicity.

Cardiovascular System Toxicity

Toxicity of the cardiovascular system occurs at plasma lidocaine concentrations much greater than those necessary to cause seizures⁴⁴; thus, cardiovascular depression is less likely to occur during lidocaine administration to horses. In conscious horses, plasma concentrations of lidocaine between 1.85 and 4.53 $\mu\text{g/mL}$ caused statistically significant changes in P-wave duration, P-R interval, R-R interval, and Q-T interval; however, these changes were within the normal reference ranges, and were not deemed to be clinically significant.¹⁰⁷ Nevertheless, lidocaine toxicity can result in hypotension, myocardial depression, and refractory cardiac dysrhythmias. We have observed severe hypotension in an experimental setting where a large dose of lidocaine (5.0 mg/kg IV) was administered over a 5-minute period to ponies anesthetized with halothane. Although hypotension was readily reversed by infusion of dobutamine in those ponies, severe lidocaine-induced cardiovascular depression may, in some cases, be resistant to conventional treatment with anticholinergic drugs and positive inotropes.

SUMMARY

The antinociceptive effects of systemic lidocaine are well documented in human beings and laboratory animals. There are few studies evaluating the efficacy of systemic lidocaine in horses; however, evidence exists for its anesthetic and antinociceptive effects in this species. Based on findings from the study of human patients, it appears that the best results are obtained when lidocaine is administered in the

perioperative period, rather than in the postoperative period only. Administration of lidocaine intraoperatively has the benefit of decreasing volatile anesthetic MAC and the potential to provide postoperative analgesia and decrease the incidence of postoperative ileus.

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