Lidocaine hydrochloride is widely used in veterinary medicine as a local anesthetic and as an anti-arrhythmic for treatment of animals with ventricular tachycardia.1,2 The use of systemically administered lidocaine has increased dramatically in equine hospitals as a treatment for horses with intestinal ileus.3–5 Lidocaine has novel anti-inflammatory properties that may also ameliorate the effects of ischemia-reperfusion injury.6–8 The purpose of the information reported here was to evaluate the current use of systemically administered lidocaine in the treatment of horses with 2 specific gastrointestinal tract problems (ie, ileus and ischemic intestinal injury).

Pharmacologic Properties of Lidocaine

All local anesthetics are composed of 3 subunits: a lipophilic aromatic group, such as a benzene ring; a hydrophilic amine group; and an intermediate chain that connects those 2 structures.9 The nature of the intermediate chain subclassifies local anesthetics into esters or amides. Lidocaine has an amide link as the intermediate bond and is therefore classified as an aminoamide local anesthetic. All amide local anesthetics, such as bupivicaine, ropivicaine, and prilocaine, have a prefix that ends with the letter i (ie, bupi-, ropi-, and pri-, respectively), whereas ester anesthetics, such as cocaine, benzocaine, and procaine, do not. The 2 classes of local anesthetics are metabolized differently. Ester anesthetics are hydrolyzed by cholinesterase in the plasma to form the metabolite para-amine benzoic acid, which is a known allergen. Amide anesthetics are primarily metabolized by the liver. Hepatic cytochrome P450 enzymes first dealkylate and then hydrolyze the compound. Lidocaine is dealkylated to the main metabolites monoethylglycinexylidide and glycinexylidide, which retain local anesthetic properties, before being hydrolyzed further.11 Because lidocaine is metabolized by the liver, serum concentrations can increase in animals with hepatic disease12 and cause toxicosis at standard administration rates.

Lidocaine acts as a local anesthetic by binding to voltage-gated sodium channels to block the influx of Na+ into a cell and hence prevent propagation of the action potential. Nonetheless, the effectiveness of sys-

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significantly less (mean of 6 days less) in lidocaine-treated horses than in saline solution–treated horses, although short-term survival did not differ significantly.

**Mechanisms of Action of Lidocaine in Ileus**

Analysis of results from the aforementioned studies suggests that there is a clinical benefit to systemic administration of lidocaine in the management of animals with ileus. However, the mechanism of action by which this effect is achieved is unclear. An in vitro study on isolated strips of intestinal muscle treated topically with lidocaine resulted in contraction of muscle obtained only from the proximal portion of the duodenum and not from the pyloric antrum or midjejunum. Additionally, systemic administration of lidocaine to clinically normal horses did not decrease the duration of the migrating myoelectrical complex, increase the number of phase III events in the migrating myoelectrical complex, or result in more frequent spiking activity, when compared with results after administration of saline solution, which would be expected if it were a prokinetic agent. Although both studies were performed in clinically normal horses and results from horses with ileus may differ, the results suggest that lidocaine does not have a direct prokinetic effect. Therefore, it is likely that the clinical effectiveness of lidocaine is attributable to other mechanisms of action.

Experiments in mice have determined the importance of intestinal inflammation as a cause of ileus 12 to 24 hours after surgical manipulation. Macrophages within the muscularis layers of the intestine are activated by surgical manipulation of the intestine, which causes them to release proinflammatory cytokines and prostaglandins. In turn, these inflammatory mediators cause influx of monocytes and neutrophils into the muscularis layers and further release of inflammatory products, which reduce muscle contractility and ultimately result in ileus. In horses, neutrophilic inflammation has been identified in the jejunum 18 hours after experimentally induced ischemia. The temporal relationship between onset of clinical signs of ileus and peak intestinal inflammation suggests that intestinal inflammation may mediate postoperative ileus in horses. Accordingly, the beneficial effects of lidocaine in the management of horses with ileus may be related to its anti-inflammatory properties.

Local anesthetics inhibit many of the immune functions of neutrophils. In vitro assays to evaluate these various functions have revealed that lidocaine inhibits neutrophil adhesion, phagocytosis, and the production of free radicals. Inhibition of these functions could reduce the deleterious effect of neutrophils on intestinal contractility, although many of these effects are only evident at plasma concentrations higher than those achieved clinically. In addition, lidocaine can reduce the expression of endothelial adhesion molecules, which is the first step in migration of neutrophils into the intestines. There is also evidence of anti-inflammatory effects of lidocaine on the intestines. In rats with experimentally induced obstructive ileus, IV administration of lidocaine prevents fluid secretion into the lumen of the small intestine and reduces edema formation in the intestinal wall. Additionally, topical administration of lidocaine gel and systemic administration of lidocaine reduce inflammation in humans with ulcerative colitis. Therefore, the beneficial effects of systemic administration of lidocaine in horses with ileus are likely attributable to anti-inflammatory effects, although additional studies are necessary to investigate this hypothesis.

**Use of Lidocaine in Ischemia-Reperfusion Injury**

Ischemic lesions of the gastrointestinal tract have a poorer prognosis than do simple obstructions. Reperfusion injury is believed to contribute further to deterioration in viability of the intestines after surgery. During reperfusion, transepithelial migration of neutrophils physically disrupts the mucosal barrier and then causes additional damage and enterocyte death via the release of free radicals and toxic substances. In horses, neutrophils accumulate in the large colon during ischemia, with further influx during the reperfusion period, which suggests that neutrophils are an important contributor to ischemia-reperfusion injury in horses. Generation of free radicals by xanthine oxidase when blood flow is restored is believed to initiate reperfusion injury in the small intestines by causing lipid peroxidation of cell membranes and generation of chemoattractants, such as leukotriene B. Increases in xanthine oxidase have been detected during ischemia in the equine small intestines, although similar increases have not been detected in the large colon. Currently, there is little information on the effectiveness of lidocaine in the management of intestinal ischemia and reperfusion in any species. Its use has been investigated in animals used experimentally to evaluate stroke, heart attack, and organ transplantation, all of which are likely to have ischemia-reperfusion injury as a central mechanism. Many studies have focused on the effect of systemic administration of lidocaine in dogs with experimentally induced myocardial ischemia and reperfusion. These studies have revealed that treatment with lidocaine reduces lipid peroxidation in membranes, reduces the size of infarcts, reduces accumulation of neutrophils, and improves subsequent cardiac contractility. Similar beneficial effects of systemic administration of lidocaine have been reported in dogs and rodents with experimentally induced cerebral ischemia and reperfusion. With regard to lung and kidney transplants, addition of lidocaine to the organ storage solution reduces reperfusion injury as evidenced by a decrease in histologic damage, a reduction of neutrophil influx into the graft, and improvements in organ function. Effects of treatment with systemically administered lidocaine in ischemic–injured equine jejunum have been evaluated. In one of those studies, systemic administration of lidocaine 15 minutes prior to reperfusion significantly reduced the mean grade for mucosal damage, compared with results after treatment with saline solution. In the other study, treatment with lidocaine ameliorated the negative effects of fluoxetine megadose on recovery of the mucosal barrier, as evidenced by a higher transepithelial resistance when the 2 treatments
Mechanisms of Action of Lidocaine in Ischemia-Reperfusion Injury

Mechanisms by which treatment with lidocaine reduces ischemia-reperfusion injury in any organ are not completely understood. As mentioned previously, influx of neutrophils from the circulation into the tissues has been associated with reperfusion injury. Similar to the effects in ileus, inhibition of neutrophil activation by lidocaine is likely to play an important role in amelioration of reperfusion injury. Isolated human neutrophils subjected to oxygen depletion and then reoxygenation have decreased expression of endothelial adhesion molecules when they are incubated with lidocaine before depletionreoxygenation. A similar effect of lidocaine is evident when isolated neutrophils from healthy volunteers are incubated with plasma from a human arm that has undergone ischemia and reperfusion by tourniquet application and release. Such adhesion molecules are also necessary for neutrophil migration across the intestinal epithelium. Therefore, a reduction in the expression of neutrophil adhesion molecules by treatment with lidocaine may reduce damage to intestinal epithelial cells by reducing neutrophil influx into the intestines during reperfusion, although this has not yet been investigated.

Integrity of the vascular endothelium is also damaged by neutrophil diapedesis, which results in leakage of plasma proteins (such as albumin) from the capillaries and a subsequent reduction in oncotic pressure and circulating plasma volume. In rats with experimentally induced endotoxemia, treatment with lidocaine before administration of endotoxin reduced adherence of leukocytes to the vascular endothelium and reduced leakage of albumin across venules, compared with results for preendotoxin treatment with saline solution.

In that study, lidocaine also prevented an endotoxin-induced decrease in mean arterial pressure. Absorption of endotoxin across intestinal mucosa that has been damaged by ischemia and reperfusion is a cause of early postoperative fatalities in many colic patients. The resulting increase in capillary permeability makes it challenging to maintain circulating plasma volume and organ perfusion. The anti-inflammatory effects of lidocaine on neutrophil adhesion may ameliorate the increase in capillary permeability evident clinically in colic patients after surgery, which ultimately would improve fluid dynamics in these patients.

Another mechanism by which lidocaine may reduce ischemic injury is prevention of ischemic-induced intracellular Na+ overload (Figure 1). The intracellular Na+ concentration increases during ischemia because of Na+ influx through the epithelial Na+ channel (which is blocked by lidocaine) and the NHE. The NHEs are responsible for electroneutral absorption of Na+ in exchange for H+ as well as regulation of intracellular pH. During ischemia, there is an increase in the concentration of H+ in cells as a result of anaerobic metabolism. Excess H+ is exported by the NHEs, which results in an increase in the intracellular Na+ concentration. The intracellular Na+ concentration is further increased because the principal mechanism for Na+ efflux from the cell (ie, Na+-K+-ATPase) is inhibited during ischemia as a result of ATP being depleted. The Na+-Ca2+ exchanger typically pumps Ca2+ out of cells in exchange for Na+ in a 1:3 ratio. However, during reperfusion, the Na+-Ca2+ exchanger reverses to expel excess Na+ from the cells, which causes Ca2+ influx and intracellular Ca2+ overload. An increase in the intracellular Ca2+ concentration is responsible for activation of many key inflammatory enzymes, including xanthine oxidase and calcium-dependent phospholipase A2, and this ultimately results in cell death.

Although these mechanisms have been predominately evaluated for myocardial and cerebral ischemia, intracellular Na+ overload is also likely to play a role in intestinal ischemic injury. In porcine ileum subjected to ischemic conditions for 45 minutes, pharmacologic inhibition of the NHE2 isoform improves the recovery of the injured mucosal barrier and reduces mucosal-to-serosal flux of Na+. Treatment with lidocaine can significantly reduce the increase in intracellular Na+ concentration during myocardial ischemia by blocking the Na+ channel.

#### Figure 1—Schematic depicting an ischemic cell and the mechanisms through which anaerobic metabolism results in an increase in the intracellular Na+ concentration. Excessive H+ from anaerobic metabolism is removed from the cell by the NHE, which results in an increase in the intracellular Na+ concentration [Na+]. In addition, an increased influx of Na+ through the epithelial Na+ channel (ENaC) is also important in toxic effects induced by ischemia. Because of the depletion of ATP during ischemia, excess Na+ cannot be removed by Na+-K+-ATPase on the basolateral border. Instead, the high [Na+] results in reversal of the Na+-Ca2+ exchanger (NCX) to expel excess Na+, which results in an increase in the intracellular Ca2+ concentration (Ca2+) and subsequent activation of inflammatory enzymes. Lidocaine may block the ENaC to prevent Na+ influx via the ENaC and ameliorate intracellular Na+ overload.

were combined, compared with effects after administration of flunixin meglumine alone.
Conclusions
An understanding of the anti-inflammatory properties of lidocaine has opened up a novel and exciting treatment option for horses with inflammatory conditions of the gastrointestinal tract, including ileus and recovery from ischemic injury. Equine clinicians principally use systemic administration of lidocaine for the management of ileus, with its effectiveness likely attributable to its ability to inhibit neutrophil activation, rather than through its actions as a prokinetic. The benefits of systemic administration of lidocaine in ischemia-reperfusion injury have been determined predominantly in other species and other organs. Its benefit in cardiac and cerebral ischemia-reperfusion injury is achieved by preventing intracellular Na⁺ overload and through its anti-inflammatory properties. Although these mechanisms have not been evaluated in ischemic-injured intestines, it is likely that the effect of lidocaine is similar in this tissue. Given the high mortality rate after colic surgery that results from the absorption of endotoxin across injured intestinal mucosa, a drug that reduces intestinal ischemia-reperfusion injury could also reduce the mortality rate in these horses. Therefore, further evaluation of the clinical effectiveness of lidocaine in horses with gastrointestinal tract disease is urgently needed.

References