

Use of intravenous lipid emulsion to treat ivermectin toxicosis in a Border Collie

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Case Description—A 2-year-old spayed female Border Collie was treated with IV lipid emulsion (ILE) after ingesting 6 mg/kg (2.73 mg/lb) of an equine ivermectin anthelmintic paste 8 hours prior to examination.

Clinical Findings—On initial examination, the dog had stable cardiovascular signs but had diffuse muscle tremors and was hyperthermic. Neurologic evaluation revealed that the dog was ataxic and had mydriasis with bilaterally absent menace responses and pupillary light reflexes. The remaining physical examination findings were unremarkable. Results of CBC, serum biochemical analysis, venous blood gas analysis, and measurement of plasma lactate concentration were also within reference limits.

Treatment and Outcome—The dog was treated with ILE in addition to supportive care with IV fluid therapy and cardiovascular, respiratory, and neurologic monitoring. The use of ILE treatment was initiated in this patient on the basis of previous clinical and experimental evidence supporting its use for toxicosis resulting from lipid-soluble agents. An initial bolus of 1.5 mL/kg (0.68 mL/lb) of a 20% sterile lipid solution was administered IV over 10 minutes, followed by a constant rate infusion of 0.25 mL/kg/min (0.11 mL/lb/min) over 60 minutes that was administered twice to treat clinical signs of ivermectin toxicosis. The dog was discharged from the hospital 48 hours after admission and was clinically normal within 4 days after ivermectin ingestion. Further diagnostic evaluation subsequently revealed that this dog was unaffected by the multidrug resistance gene (*MDR-1*) deletion, known as the ATP-binding cassette polymorphism.

Clinical Relevance—Ivermectin toxicosis in veterinary patients can result in death without aggressive treatment, and severe toxicosis often requires mechanical ventilation and intensive supportive care. This is particularly true in dogs affected by the ATP-binding cassette polymorphism. Novel ILE treatment has been shown to be effective in human patients with lipid-soluble drug toxicoses, although the exact mechanism is unknown. In the patient in the present report, ILE was used successfully to treat ivermectin toxicosis, and results of serial measurement of serum ivermectin concentration supported the proposed lipid sink mechanism of action. (*J Am Vet Med Assoc* 2011;239:1328–1333)

A 2-year-old spayed female (17.8-kg [39.2-lb]) Border Collie was admitted to the Emergency Service at the Matthew J. Ryan Hospital at the University of Pennsylvania for treatment and monitoring after ingesting a toxic amount of ivermectin. Approximately 5 hours prior to examination by the referring veterinarian, the dog had ingested a new, unopened 6.08-g (0.21-oz) tube of 1.87% ivermectin equine dewormer paste.^a The referring veterinarian noted clinical signs of lethargy, ataxia, tremors, inability to walk without support, and blindness on clinical examination. At this time, Pet Poison Helpline^b was contacted for consultation on management. On the basis of the dog's breed susceptibility to ivermectin toxicosis^{1–5} and concern for a possible *MDR-1* allele mutation,^{1–4} now known as the

ABBREVIATIONS

CPA	Cardiopulmonary arrest
CRI	Constant rate infusion
ILE	Intravenous lipid emulsion
PLR	Pupillary light reflex

ABCBI-1Δ polymorphism,³ as well as the large total ingested dose of 6 mg/kg (2.73 mg/lb), emergency transfer to a 24-hour facility equipped to provide intensive care and neurologic monitoring was recommended. The use of novel treatment with ILE was also recommended as a potential antidote for toxicosis from this lipid-soluble drug.

The dog was transferred to the Matthew J. Ryan Hospital at the University of Pennsylvania Emergency Service for further treatment and observation approximately 8 hours after ivermectin ingestion. Initial physical examination revealed increased rectal temperature (40.3°C [104.6°F]), pink and moist mucous membranes, unremarkable results of thoracic and cardiac auscultation, strong and synchronous femoral pulses, and no abnormalities on abdominal palpation. Results of fundic examination were unremarkable. Neurologic examination revealed depressed but responsive menta-

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tion, bilateral mydriasis with absent direct and consensual PLR, and absent menace and dazzle response in each eye. The dog also had diffuse muscle tremors and was nonambulatory. Further examination revealed that the dog was mildly hypertensive, with an initial systolic arterial blood pressure of 163 mm Hg, diastolic arterial blood pressure of 70 mm Hg, and mean arterial pressure of 114 mm Hg. Because of the severity of the muscle tremors, an accurate pulse oximetry reading could not be obtained. Results of an initial CBC, serum biochemical analysis, and venous blood gas analysis and serum electrolyte concentration, plasma lactate concentration, PCV, and total solids concentration were all within reference limits. Because of the experimental nature of ILE treatment in veterinary medicine as well as the theoretical risks for potential adverse events, possible complications, and the extralabel nature of use were discussed with the owner. Consent for novel treatment with ILE as needed during the course of hospitalization was given.

A left cephalic IV catheter had been previously placed by the referring veterinarian and was used for the administration of crystalloid fluid therapy at a maintenance rate of 2 mL/kg/h (0.91 mL/lb/h)^c IV because it was anticipated that the patient would not eat or drink initially while in the hospital. A second IV catheter was placed in the right cephalic vein by use of a strict aseptic technique, including surgical scrub, draping, and sterile gloves. This catheter was reserved for infusion of ILE only. A 20% sterile, nonpyrogenic lipid solution was used.^d As this lipid solution^d is isosmotic (osmolarity, 258 mOsm/L), administration through a peripheral catheter was considered safe, therefore central venous access was not required.

Prior to initiating the infusion of ILE, 5 mL of whole blood was collected and separated for measurement of serum ivermectin concentration. On the basis of recommendations from Pet Poison Helpline,^b a bolus of 20% lipid solution (1.5 mL/kg [0.68 mL/lb], IV) was administered over 10 minutes, followed by a CRI (0.25 mL/kg/min [0.11 mL/lb/min], IV) for 60 minutes. Blood was collected for measurement of serum ivermectin concentration immediately after the bolus ILE treatment, 30 minutes into the CRI, immediately following the CRI, and 6 hours after completion of the CRI. All serum samples were submitted for analysis, and ivermectin concentrations were measured by use of liquid chromatography–mass spectrometry (Table 1).^e

The dog's neurologic status, temperature, respiratory status, and cardiovascular status were monitored every 2 to 4 hours. The dog's neurologic status initially remained unchanged. Six hours after the start of the ILE treatment, the dog became more responsive and ambulatory but remained ataxic. The dog continued to have diffuse muscle tremors, but a return of a dazzle light response was noted bilaterally by 6 hours after the initiation of ILE treatment. Concurrently, results of repeated venous blood gas analysis and serum electrolyte concentration, plasma lactate concentration, PCV, and total solids concentration remained within reference limits; however, the presence of grossly visible lipemia was detected in the patient's serum. In addition, the dog's rectal temperature (38.8°C [101.8°F]), oxygen saturation as measured

by use of pulse oximetry (96%; reference range, 95% to 100%), heart rate, and blood pressure measurements remained within reference limits. Twelve hours after the start of the initial ILE bolus, the lipemia had resolved. Despite some improvement in clinical signs, an additional ILE infusion was elected because there was some improvement after the initial treatment and owner financial constraints prohibited prolonged hospitalization. Blood was again collected before and immediately after the second infusion for determination of serum ivermectin concentrations (Table 1). By 15 hours after the start of the first ILE bolus and 1.5 hours after completion of the second ILE infusion, the dog was bright and alert and had minimal tremors, improved mydriasis, and weak but incomplete PLR. By 19 hours after the start of the first ILE bolus and 5.5 hours after completion of the second ILE infusion, the dog had complete resolution of tremors and an inconsistent menace response.

Twenty hours after initiation of the first 20% lipid solution^d bolus, a consultation by the neurology service confirmed the most recent neurologic findings of an inconsistent menace response, incomplete PLR, and resolved tremors, in addition to mild hyperreflexia in all limbs, which was attributed to the patient's nervous demeanor when held in lateral recumbency. Supportive care, including continued monitoring and maintenance IV fluid therapy (2 mL/kg/h),^c was continued. At this time, the dog was also readily eating when hand-fed. Neurologic, cardiovascular, and respiratory monitoring was continued for an additional 24 hours. The dog's ataxia almost completely resolved, and there were mild subjective improvements in visual ability and PLR completeness. As the dog continued to eat and drink without assistance, IV fluid therapy was discontinued. The dog was discharged to its owner 48 hours after initial examination at the referral hospital. Follow-up phone calls were performed daily for 2 days, at which point the owner thought the dog's clinical signs had completely resolved, including return of vision. Prior to discharge, a buccal mucosal brush sample was collected for ABCB1 genotyping.^f The dog was found to be unaffected by the ABCB1-1Δ polymorphism.

Table 1—Serum ivermectin concentrations in a 2-year-old spayed female Border Collie (body weight, 17.8 kg [39.2 lb]) at intervals before, during, and after treatment with ILE (20% lipid solution, IV)* as determined by use of liquid chromatography–mass spectrometry.

Blood sample	Time since ivermectin ingestion (h)	Ivermectin concentration (μg/mL)
Prior to first ILE bolus	8	6.84
After first ILE bolus	8.25	7.85
30 min into first ILE CRI	8.75	5.33
Immediately after first ILE CRI	9.25	4.56
6 h after completion of first ILE CRI	15.25	2.42
Immediately before second ILE bolus	20	1.42
Immediately after second ILE CRI	21.25	2.61

The dog had ingested 6 mg/kg (2.73 mg/lb) of an equine ivermectin anthelmintic paste^g 8 hours prior to initial examination at Matthew J. Ryan Veterinary Hospital.

*A bolus of 20% lipid solution (ILE; 1.5 mL/kg [0.68 mL/lb]) was administered over 10 minutes, followed by a CRI (0.25 mL/kg/min [0.11 mL/lb/min]) for 60 minutes. A second treatment using the same bolus and CRI protocol was repeated 12 hours after commencement of ILE treatment (initial ILE bolus).

Discussion

Ivermectin, a widely used broad-spectrum antiparasitic drug, is a macrocyclic lactone derived from *Streptomyces* sp, a soil-dwelling actinomycete. It is a highly lipophilic drug that is rapidly absorbed after ingestion, with peak plasma concentrations reached 3 to 5 hours after therapeutic dosing.^{6,7} It is extensively distributed to many tissues because of its lipophilic nature, with a long terminal half-life of 80.3 ± 29.8 hours because of enterohepatic recirculation. Ivermectin is largely excreted in feces (> 90%) and urine (< 2%) as an unmetabolized parent compound.^{6,7} Ivermectin binds to glutamate-gated chloride channels and γ -aminobutyric acid-gated chloride channels in nematode motor and sensory neurons, with the motor neurons located in the pharynx being most important. Drug binding causes slow, irreversible channel opening and subsequent hyperpolarization or depolarization, which ultimately leads to neuronal dysfunction and death.⁸ Toxicosis in veterinary patients is likely a result of ivermectin binding and resultant presynaptic release and postsynaptic binding of γ -aminobutyric acid, leading to potentiation of the inhibitory neurotransmitter's effects within the CNS.⁸ A large glycosylated transmembrane transporter, p-glycoprotein, has been identified in many tissues, including the small intestine and colon, brush border of renal proximal tubules, canalicular surfaces of hepatocytes, and apical and luminal endothelial cells of the capillaries in the CNS.⁹ The role of p-glycoprotein in the CNS is to limit drug penetration, and it is this mechanism that prevents neurotoxicity in mammals treated therapeutically with ivermectin and other macrocyclic lactones.⁹

A 4-base pair deletion in the ABCB1-1 Δ transporter causes a frame shift mutation and premature termination of p-glycoprotein synthesis.¹⁻³ Collies and related herding breeds of dogs that are homozygous for the mutation have increased sensitivity to ivermectin and related antiparasitic drugs as well as other drugs, requiring the p-glycoprotein to limit CNS penetration because of accumulation of high drug concentrations in the CNS.¹⁻³ The deletion has been reported in Collies, Australian Shepherds, Border Collies, Shetland Sheepdogs, a German Shepherd Dog, and other rare breeds of sighthound origin.¹⁻⁵

Ivermectin toxicosis is well described in the veterinary literature^{1,5-17} and usually occurs following an overdose of a small animal ivermectin product, accidental ingestion, or inappropriate administration of a formulation intended for large animal species or because of appropriate dosing in an animal affected by the ABCB1-1 Δ polymorphism. Clinical signs reported to result from ivermectin toxicosis include lethargy, vomiting, ataxia, mydriasis, blindness, retinopathy, tremors, seizures, coma, and respiratory failure.^{5,10-17} Dogs without the ABCB1-1 Δ polymorphism generally tolerate oral ivermectin dosages of up to 2.5 mg/kg (1.14 mg/lb) before clinical signs of toxicosis occur, with the LD₅₀ in clinically normal Beagles reported as 80 mg/kg (36.36 mg/lb).¹⁸ In comparison, in dogs affected by the multidrug resistance gene (*MDR-1*) with ABCB1-1 Δ polymorphism, the LD₅₀ is 0.15 to 0.20 mg/

kg (0.07 to 0.09 mg/lb).¹⁹ Treatment of patients with known or suspected ivermectin overdose is generally considered supportive and includes induction of emesis and administration of activated charcoal in patients with appropriate neurologic status or no clinical signs, IV fluid therapy, supplemental oxygen, seizure control, and mechanical ventilation for respiratory failure.^{5,10-19} Given the long terminal half-life of 80.3 ± 29.8 hours for ivermectin,^{6,7,18} treatment for days to weeks may be required, resulting in substantial financial implications for the pet owners.^{5,10-16,19}

Intravenous lipid emulsion was initially used in the early 1960s for nutritional support in the form of both total and partial parenteral nutrition and later became used as a vehicle for drug delivery for emulsions (eg, propofol).²⁰ In the 1970s and 1980s, experimental studies of rabbits and rats showed early support for its use with certain drug toxicoses (including chlorpromazine, cyclosporine, and phenytoin).²¹ Twenty years later, Weinberg et al^{22,23} reintroduced the use of ILE for certain drug toxicoses. In experimental studies of both rats²² and dogs²³ with bupivacaine-induced CPA, the administration of ILE increased the total LD₅₀ in rodents and improved overall survival rate in dogs. In the study²³ of anesthetized dogs with CPA induced with bupivacaine (10 mg/kg [4.5 mg/lb], IV), lipid infusion after 10 minutes of cardiopulmonary cerebral resuscitation improved hemodynamic variables and survival rate, compared with results for saline (0.9% NaCl) solution-treated dogs. Since these studies, numerous case reports and case series in the human medical literature have reported the success of ILE treatment; however, success often ranged from mild improvement to complete resolution of clinical signs. This variability was likely because of lipophilicity, or lipid solubility, of the toxin as well as variability in ingested dose, time between exposure and treatment initiation, and concurrent health conditions of the affected patient. Today, ILE administration has emerged as an antidote of choice for toxicoses involving lipid-soluble agents in which CPA and appropriate resuscitation alone have failed to result in the return of spontaneous circulation. Clinical reports of human patients and animal experimental studies have also explored the use of ILE infusion with a variety of other drug toxicoses, including chlorpromazine,²¹ bupivacaine²²⁻²⁷ and levobupivacaine,²⁸ verapamil,^{29,30} clomipramine,³¹ propanolol,³² mepivacaine,^{24,33} ropivacaine,^{24,34} bupropion,³⁵ lamotrigine,³⁵ haloperidol,³⁴ quetiapine,³⁶ sertaline,³⁶ doxepin,³⁷ carvedilol,⁸ amlodipine,³⁸ and nebivolol.³⁹ The use of ILE treatment has been shown to be beneficial when combined with standard resuscitation efforts in restoring hemodynamic status, particularly blood pressure, compared with standard resuscitation efforts alone.^{20-23,29,30,40} However, because the indications for ILE treatment in human medicine are currently limited to catastrophic toxicoses with CPA, no prospective, randomized studies exist.

Currently, the exact mechanism of action for ILE treatment for toxicoses resulting from lipid-soluble agents is unknown. Three proposed mechanisms include augmentation of cardiac function by providing energy in the form of lipid to the myocytes, restoration

of myocardial function via increased intracellular calcium concentrations, and the creation of a lipid partition or lipid sink within the intravascular space and preferential sequestration of lipophilic drugs into the newly formed compartment.^{41–44} Experimental studies evaluating the solubility of local anesthetics demonstrated high capacity for drug binding by the lipid emulsions, supporting the lipid sink theory.⁴⁵ In a study⁴⁶ of clomipramine toxicosis in rabbits, ILE-induced resolution of hypotension secondary to toxicosis was associated with increased concentrations of clomipramine in the plasma and a decreased volume of distribution.⁴⁶ In a case report³⁵ of drug-induced CPA from both lamotrigine and bupropion ingestion in a human patient, the serum concentration of bupropion 6.5 hours after ingestion was 180 ng/mL (fatal overdose concentration range, 430 to 446 ng/mL). The patient had a seizure and developed CPA approximately 10 hours after ingestion of bupropion and lamotrigine, at which time the serum concentrations of bupropion and lamotrigine were unknown. At 11.5 hours after ingestion and 52 minutes into unsuccessful cardiopulmonary cerebral resuscitation and advanced cardiac life support for CPA, a 100-mL bolus (1.8 mL/kg [0.82 mL/lb]) of 20% ILE was given, and within 1 minute afterward, return of spontaneous circulation (palpable pulses) occurred. One hour and 15 minutes after administration of the lipid infusion, bupropion serum concentration was 880 ng/mL. Whereas serum bupropion concentration immediately prior to treatment with ILE was not measured, the almost 5-fold increase in the serum bupropion concentration after treatment supports a possible lipid sink where bupropion was pulled from sites of tissue distribution back into this intravascular lipid compartment. By 18.25 hours after ingestion, the bupropion serum concentration decreased to 390 ng/mL and further decreased to 62 ng/mL by approximately 30 hours after ingestion. This patient survived to discharge from the hospital approximately 1 month later, despite pulmonary complications.³⁵

Acute reactions, such as fever, vomiting, tachypnea, dyspnea, and hyperlipidemia, have been reported with ILE use in humans.^{43,47} Other concerns regarding ILE treatment include bacterial contamination of the lipid-rich emulsion, phlebitis, and fat embolism. Finally, potential anaphylactic reactions can be seen within 20 minutes after administration of ILE in humans, but the occurrence is rare and reported to be < 1%.⁴³ None of these adverse effects have been reported to date in experimental animal studies.^{25–27,34–39,43,47–49,g}

In clinical veterinary medicine, novel ILE treatment has been previously reported in a puppy after moxidectin overdose.³⁰ A 16-week-old sexually intact female Jack Russell Terrier was examined for seizures, subsequent paralysis, and coma after suspected ingestion of a moxidectin-containing equine anthelmintic product. In addition to supportive care, including mechanical ventilation, a bolus of 20% ILE (2 mL/kg) was administered 10 hours after exposure, followed by a CRI (0.067 mL/kg/min [0.03 mL/lb/min], IV) for 4 hours, which resulted in mild improvement. An additional CRI (0.5 mL/kg/min [0.23 mL/lb/min], IV) for 30 minutes was started 25.5 hours after exposure, which normalized the puppy's neu-

rologic status within 6 hours after completion of the second CRI. Serum samples obtained 30 minutes after the second lipid infusion had positive results for moxidectin but negative results for ivermectin (negative detection limit, 10 µg/kg)^h via liquid chromatography–mass spectroscopy, even though the dog had been treated for 30 days previously with 1 mg of ivermectin PO once daily for the prevention of demodicosis.³⁰ Whereas the serum moxidectin concentration confirmed ingestion, without serial determination of serum concentration both before and during ILE treatment, it is not possible to determine the change in rate of moxidectin clearance attributable to the lipid emulsion nor is it possible to ascertain which of the proposed mechanisms of action of ILE administration were responsible for the reported clinical response to this treatment.

In the patient reported here, the increase in serum ivermectin concentrations immediately after both lipid infusions supports sequestration of the drug from tissues with high lipid content into a lipid phase created within the intravascular space and is therefore possibly supportive of the lipid sink mechanism of action. The initial increase and subsequent decrease in the serum ivermectin concentrations are also consistent with serum drug concentrations seen in the clomipramine experimental study of rabbits⁴⁶ and case report³⁵ of bupropion and lamotrigine overdose in the human patient.

Whereas the dog in the present report eventually was confirmed to be unaffected by ABCB1-1Δ polymorphism, this particular dog was treated aggressively with novel ILE because of the severity of clinical signs, its breed predilection, and its unknown ABCB1-1Δ polymorphism status at the time of initial examination. Treatment with ILE in this dog was considered safe without any adverse effects noted and may have decreased the duration of hospitalization. However, the role of ILE treatment in improving case outcomes of dogs affected by the ABCB1-1Δ polymorphism with clinical signs caused by macrocyclic lactone toxicosis remains to be determined.

Given the limited data available on ILE use in veterinary medicine and because ILE use in human patients is typically reserved as a treatment of last resort (eg, only administered after the patient has had CPA and failed to respond to traditional, aggressive advanced cardiac life support), the ideal dose and timing of ILE treatment in veterinary medicine are currently unknown. The current recommendations for ILE use in human patients, which are based on experimental studies of bupivacaine toxicosis in dogs²³ and rats,²² entail administration of a bolus of 20% ILE (1.5 mL/kg, over 1 minute) followed by a CRI (0.25 mL/kg/min) for 30 to 60 minutes. The bolus can then be repeated 1 to 2 times if there is no response to treatment, and the CRI can be increased to 0.50 mL/kg/min (0.23 mL/lb/min) if hypotension results.⁴⁹ The duration of time for which ILE treatment could be effective after ingestion of a toxic dose of a lipophilic agent is unknown and likely related to the rate of the drug's metabolism and the patient's cardiovascular and perfusion status as well as the presence of concurrent diseases or organ dysfunction.

Whereas novel ILE use with fat-soluble agents may be effective, safety data are lacking in veterinary pa-

tients. Until further safety and dosage information is determined, the judicious use of ILE treatment should be limited to severely affected, critically ill patients and not to routine treatment of poisoned patients that are already responding to currently recommended treatments. However, preliminary results on the use of ILE treatment in veterinary medicine as a relatively inexpensive, generally safe antidote for lipid-soluble toxicosis appear promising and warrant further investigation.

- a. Bimectin Inc, Riverside, Mo.
- b. Pet Poison Helpline, Minneapolis, Minn.
- c. Plasmalyte A, Baxter Healthcare Corp, Deerfield, Ill.
- d. Liposyn III 20%, Hospira Inc, Lake Forest, Ill.
- e. Pennsylvania Animal Diagnostic Laboratory System (PADLS), New Bolton Center Toxicology Laboratory, Kennett Square, Pa.
- f. Washington State University College of Veterinary Medicine Veterinary Clinical Pharmacology Laboratory, Pullman, Wash.
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- h. Poppenga R, California Animal Health & Food Safety Laboratory System, Davis, Calif. Personal communication, 2010.

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From this month's AJVR

Effects of in vivo lidocaine administration at the time of ischemia and reperfusion on in vitro contractility of equine jejunal smooth muscle

Maria Guschlbauer et al

Objective—To determine whether administration of lidocaine during ischemia and reperfusion in horses results in concentrations in smooth muscle sufficient to protect against the negative consequences of ischemia-reperfusion injury on smooth muscle motility.

Animals—12 horses.

Procedures—Artificial ischemia and reperfusion injury of jejunal segments was induced in vivo in conjunction with lidocaine treatment during ischemia (IRL) or without lidocaine treatment (IR). Isometric force performance was measured in vitro in IRL and IR smooth muscle preparations with and without additional in vitro application of lidocaine. Lidocaine concentrations in smooth muscle were determined by means of high-performance liquid chromatography. To assess the influence of lidocaine on membrane permeability, activity of creatine kinase and lactate dehydrogenase released by in vitro incubated tissues was determined biochemically.

Results—In vivo administration of lidocaine allowed maintenance of contractile performance after an ischemia and reperfusion injury. Basic contractility and frequency of contractions were significantly increased in IRL smooth muscle tissues in vitro. Additionally, in vitro application of lidocaine achieved further improvement of contractility of IR and IRL preparations. Only in vitro application of lidocaine was able to ameliorate membrane permeability in smooth muscle of IR and IRL preparations. Lidocaine accumulation could be measured in in vivo treated samples and serum.

Conclusions and Clinical Relevance—In vivo lidocaine administration during ischemia and reperfusion had beneficial effects on smooth muscle motility. Initiating lidocaine treatment during surgery to treat colic in horses may improve lidocaine's prokinetic features by protecting smooth muscle from effects of ischemia and reperfusion injury. (*Am J Vet Res* 2011;72:1449–1455)



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