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Use of intravenous lidocaine to prevent reperfusion injury and subsequent multiple organ dysfunction syndrome

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Abstract

Objective: The objective of this article is to review the human and veterinary literature and provide evidence for the potential beneficial effects of intravenous (IV) lidocaine hydrochloride in preventing post-ischemic–reperfusion injury, the systemic inflammatory response syndrome (SIRS), and subsequent multiple organ dysfunction syndrome (MODS).

Human data synthesis: Lidocaine is a local anesthetic and antiarrhythmic agent that has been used for years in human and veterinary medicine for the treatment of ventricular dysrhythmias associated with blunt cardiac trauma, myocardial ischemia, and cardiac surgery. More recently, the drug has been touted as a scavenger of reactive oxygen species (ROS), and has been used to prevent reperfusion dysrhythmias after treatment of myocardial infarction, cross-clamping of the aorta, and in trauma medicine.

Veterinary data synthesis: Although no clinical experiments with prophylactic intravenous lidocaine exist in veterinary medicine, there is a large body of evidence from experimental animals that support the use of lidocaine as a Na^+/Ca^{2+} channel blocker, superoxide and hydroxyl radical scavenger, inflammatory modulator, and potent inhibitor of granulocyte functions. Lidocaine is being used in some clinical situations in an attempt to prevent the SIRS in veterinary trauma patients.[a,b]

Conclusions: A large body of experimental evidence exists supporting the use of lidocaine as an anti-oxidant and inflammatory modulator useful in preventing reperfusion injury. With the lack of cost-effective and safe treatments for reperfusion injury in veterinary and human trauma medicine, the use of IV lidocaine to prevent the ensuing inflammatory response and MODS makes it an attractive addition to existing treatments. Therefore, it is essential that prospective clinical trials involving lidocaine as a treatment for prevention of reperfusion injury be performed in companion animals to demonstrate its safety and efficacy.

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Introduction: Pathophysiology of Reperfusion Injury

As the rapidly emerging field of veterinary emergency medicine and critical care enters a new century, great advances in the treatment of shock and inadequate tissue perfusion have been made. In a fashion similar to human medicine, these advances have led to the paradoxical realization that during reperfusion, molecules (most accurately termed 'reactive oxygen species' (ROS)) are formed and released into previously ischemic tissues.[1,2] Reactive oxygen species have an unpaired electron in the outer shell; thus, they are highly unstable (and destructive). When ROS interact with cell membranes, they damage proteins, DNA, and RNA, and cause lipid peroxidation of these membranes which leads to cell death.[2] This cellular damage caused

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by the liberation of ROS and other inflammatory mediators after reperfusion of previously viable ischemic tissues is defined as ischemia–reperfusion (I-R) injury.[1]

The mechanisms involved in the generation of ROS and subsequent I-R injury have been well described in the literature.[1,2] The best described of these mechanisms include (1) generation of superoxide radicals following the conversion of xanthine dehydrogenase (XD) to xanthine oxidase (XO), (2) hydroxyl radical production via the iron-catalyzed Haber–Weiss reaction, (3) superoxide radicals from polymorphonuclear neutrophils (PMNs), and (4) endothelial and mitochondrial dysfunction from activated leukocytes. A brief introduction to I-R and how it relates to multiple organ dysfunction syndrome (MODS) follows.

Prolonged tissue ischemia results in certain well-known cellular metabolic changes, such as decreases in oxidative phosphorylation and a failure to resynthesize energy-rich phosphates. Breakdown of purines such as ATP during ischemia leads to excessive calcium influx. Increases in intracellular calcium due to Na^+/Ca^{2+} exchange inhibition during ischemia, particularly in calcium-sensitive tissues such as the heart and brain, lead to the formation of ROS and subsequent I-R injury. One postulated mechanism for this ROS formation after calcium influx is the XD/XO pathway. Calcium ion redistribution from the mitochondria to the cytosol during ischemia is believed to activate calpain, the enzyme that converts XD to XO (Figure 1).[2] Reperfusion of tissue with oxygen then leads to the formation of large amounts of superoxide radical.[1] This calcium accumulation during ischemia is postulated to come from increased movement of calcium from the sarcoplasmic reticulum and from the extracellular space into the cytosol. One mechanism for increased cytosolic calcium is through the Na^+/Ca^{2+} exchanger. Inadequate energy substrate leads to failure of the Na^+/K^+ ATPase pump and increased extracellular Na^+, which then drives the Na^+/Ca^{2+} exchanger in reverse, increasing both intracellular Na^+ and Ca^{2+}. The formation of superoxide radical after calcium influx then quickly leads to the formation of other toxic radicals such as hydroxyl radical, hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), and peroxynitrite radicals, which are released into the systemic circulation. The most toxic of these radicals is the hydroxyl radical, which is formed through the iron-catalyzed Haber–Weiss reaction (Figure 1). Hydroxyl radical and other ROS are potent oxidizing agents that directly damage cellular membranes by oxidizing or denaturing proteins and lipids. Lipid peroxidation occurs when any free radical abstracts a methylene hydrogen atom from an unsaturated fatty acid and then forms a subsequent lipid alkyl radical.[2] The reaction of these radicals with the intracellular unsaturated fatty acids present in the cell produces unstable end products that further damage cell membranes.[2] In addition, ROS stimulate leukocyte activation and chemotaxis through the liberation of phospholipase A_2 (PLA_2) to form arachidonic acid, which then leads to the secretion of more inflammatory mediators downstream (e.g., prostaglandins, leukotrienes, thromboxanes, platelet activating factor (PAF)) (Figure 1).[1] Finally, these activated leukocytes interact with the vascular endothelium via a series of distinct steps characterized by leukocyte 'rolling', firm adherence of leukocytes to the endothelium and endothelial transmigration.[1] I-R injury initiates an increase in the expression of various endothelial adhesion molecules, which results in intermittent leukocyte–endothelial binding or 'leukocyte rolling'. Subsequent interaction of leukocyte β_2 integrins such as CD11a/CD18 with constitutively expressed endothelial adhesion molecules results in firm leukocyte adherence and aggregation.[1] Activated leukocytes then transmigrate through endothelial cell junctions and, on reaching the extravascular compartment, they release even more toxic ROS, proteases and elastases, resulting in increased microvascular permeability, edema, thrombosis, and parenchymal cell death.[1]

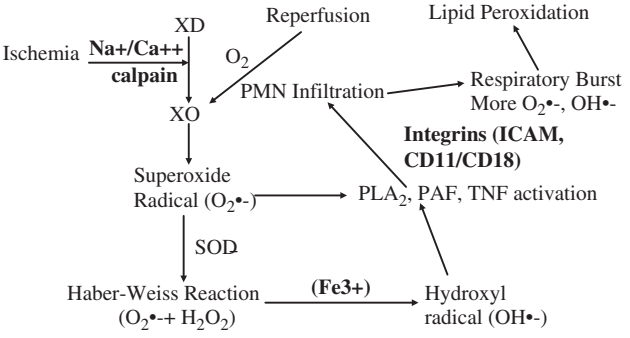

Figure 1: Mechanisms of ROS formation. XD = xanthine dehydrogenase; XO = xanthine oxidase; SOD = superoxide dismutase; H_2O_2 = hydrogen peroxide; PLA_2 = phospholipase A_2; PAF = platelet-activating factor. TNF = tumor necrosis factor.

Clinical Syndromes Associated With I-R Injury

The generation of ROS and other inflammatory mediators into the systemic circulation in response to I-R injury results in various clinical manifestations such as cardiac dysrhythmias,[1,3] central nervous system (CNS) injury,[1,4] and gastrointestinal injury[1,5] leading to MODS and death. MODS is a leading cause of death in critically ill human and veterinary patients[1,6] and may be a consequence of I-R injury of the intestine,

liver, and skeletal muscle, as well as aortic occlusion–reperfusion and the resuscitation from circulatory shock.[1] After the generation of ROS into the systemic circulation, intestinal I-R injury causes increased intestinal permeability and subsequent microbial invasion through bacterial translocation.[1,7] This results in the clinical manifestations of the systemic response (known as systemic inflammatory response syndrome or SIRS), including fever, tachycardia, tachypnea, neutrophilia, or neutropenia.[6] The target organs for this systemic response are the heart, lungs, brain, intestine, other abdominal organs (liver, kidney), the vasculature, and the coagulation system. This sequence of pathologic events then leads to the above-mentioned MODS, which is frequently heralded by pulmonary injury leading to respiratory distress, respiratory failure, and death.[1]

Animal Models of Reperfusion Injury

As we have learned more about how ROS and other inflammatory mediators are formed and gain access to systemic circulation, it has become clear that if these deleterious biochemical processes could be slowed or arrested, a substantial decrease in tissue injury and subsequent MODS would be seen. This has led to many different animal models of I-R injury and its clinical manifestations in order to begin to ascertain if any treatments could arrest the effect of I-R on various tissues and organs. Various different compounds (XO inhibitors, iron chelators, antioxidants, 21-aminosteroids, mannitol, dimethylsulfoxide) have been shown to decrease the formation of ROS or have the ability to 'scavenge' ROS, thereby decreasing lipid peroxidation and cell death.[2]

Clinically relevant veterinary diseases, which have also been documented as models of I-R injury, include traumatic brain injury, which causes CNS I-R injury,[1] I-R after cardiopulmonary resuscitation,[8] gastric-dilatation volvulus (GDV), which causes both cardiac and intestinal I-R injury,[9] strangulation obstruction in the horse,[10] and neonatal necrotizing enterocolitis (NNEC), which occurs after hypothermia or hypoxia in foals and pigs.[11]

Potential for therapeutic intervention

There are numerous classes of drugs or other agents that can have an effect on arresting I-R injury; however, most of the evidence of their mechanism of action comes from various animal model studies. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH) are all known to decrease the formation of toxic ROS through 'scavenging' them or interfering with major enzyme pathways previously discussed. In one study involving cardiac I-R injury, SOD and CAT restricted the activation of ROS by 16–18%.[2] Anti-oxidant vitamins such as vitamin E lessen the effects of lipid peroxidation by interrupting the chain reaction and intercepting radicals by binding to the cell membrane,[2] and have been shown in numerous studies to attenuate I-R.[1]

The most current theory of I-R injury in the brain is that sequential pathologic mechanisms such as Na^+/Ca^{2+} exchange inhibition, followed by *N*-methyl-D-aspartate (NMDA) receptor activation, glutamate release, ROS formation, and PMN infiltration, are all responsible for secondary I-R-mediated brain injury.[12] In a canine incomplete global ischemia model, investigators tested the hypothesis that a novel competitive NMDA receptor antagonist GPI 3000 (GPI) would ameliorate metabolic injury and that the effectiveness of the iron chelator and antioxidant, desferoxamine[c] (DFO), would be augmented by combined therapy with GPI after incomplete global cerebral ischemia. Their results indicated that both NDMA antagonism and iron chelation were needed for recovery from I-R.[13] Altered Na^+/Ca^{2+} exchange, elevated intracellular calcium levels during ischemia, and subsequent ROS formation during reperfusion may be the initial events in the I-R pathway. In a recent study, the effects of SEA0400, another novel Na^+/Ca^{2+} exchange inhibitor, on reperfusion injury *in vitro* and *in vivo* were examined. SEA0400 attenuated a Ca^{2+} challenge-induced ROS production and reduced infarct volumes in an experimental model of brain I-R injury.[14]

In experimental models of canine GDV (an excellent model of intestinal and cardiac reperfusion injury), hydroxyl radical production and PMN infiltration of ischemic tissues were implicated as causes of the gastric/cardiac necrosis. Previous studies have shown that administration of certain compounds ameliorates gastric and cardiac necrosis in surgically induced GDV.[9,15] Pharmacologic intervention studies in GDV have shown that DFO (a potent iron chelator and hydroxyl radical scavenger) and U74006F (a 21-aminosteroid), if given before decompression and subsequent reperfusion, significantly ameliorate the gastric and cardiac effects of reperfusion injury.[9,15] This was evidenced by increased survival rate, decreased levels of tissue malondialdehyde (an indicator of lipid peroxidation), and decreased pathologic evidence of gastric and cardiac tissue injury. Furthermore, administration of DFO to dogs with experimentally induced GDV completely prevented myocardial necrosis, which was evident in 5 out of 6 controls, thereby supporting the fact myocardial necrosis may be due to the iron-catalyzed Haber–Weiss reaction and subsequent hydroxyl radical release during reperfusion (Figure 1).[15]

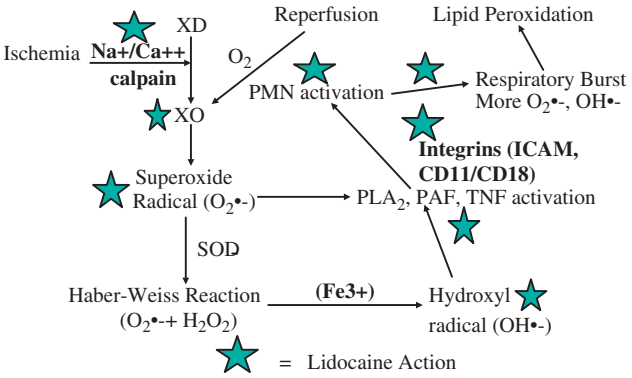

Figure 2: Mechanisms of lidocaine action. See Figure 1 for an explanations of the abbreviations. ★ = lidocaine action.

It is likely that some of the mechanisms of I-R injury that occur in the canine heart after GDV involve an increase in Ca^{2+} accumulation (as is true in the brain), and subsequent activation of XO by the mechanisms previously discussed. Experimental work in canine, porcine, and rabbit myocardial ischemia models demonstrates that pretreatment of the subjects with Ca^{2+} channel blockers such as nifedipine and clevidepine, or Na^+/H^+ exchange inhibitors, decreases postischemic ventricular dysrhythmias and infarct size.[16–19] It is theorized that Ca^{2+} follows Na^+ into ischemic tissues, so that Na^+ exchange inhibition by drugs that inhibit either Na^+/Ca^{2+} or Na^+/H^+ likely causes a similar inhibition of Ca^{2+} accumulation.[18] It is evident from these experiments, as well as others, that suppression of Ca^{2+} accumulation in myocardial tissue inhibits myocardial infarct size.

In equine medicine, although strangulating obstruction of the bowel is likely mediated through I-R injury and ROS formation,[10] studies with various compounds (DMSO, allopurinol, 21-aminosteroids) have failed to ameliorate the injury.[20,21] Although neutrophils have been shown to accumulate in the equine colon after I-R and cause injury, and are felt to be a significant source of ROS in the intestine,[22] no studies have been performed with any compounds, which would lessen the effects of the neutrophil infiltration and subsequent tissue injury.

Neonatal necrotizing enterocolitis (NNEC) is a devastating intestinal ischemic disease of preterm infants, which also occurs in newborn piglets and neonatal foals.[11] Experimental models have implicated intestinal I-R as part of its pathogenesis after significant hypoxia or hypothermia, which causes decreased intestinal blood flow and ischemia. In a hamster model with NNEC, 4 hours of mild hypothermia caused a 63% decrease in intestinal XD, along with significant histopathologic evidence of intestinal tissue injury, which was postulated to come from XO-induced superoxide release. Transmission electron microscopy of intestinal tissue verified that reperfusion injury caused significant bacterial translocation in hamster large intestinal segments.[23] It is postulated that in susceptible organs such as the intestine, I-R injury causes certain leukocyte–endothelial cell interactions, which lead to a disruption of the epithelial barrier, increased intestinal permeability, bacterial translocation, and an overwhelming inflammatory response in the general circulation.[1] In an attempt to ascertain whether previously demonstrated intestinal injury in neonatal piglet models of NNEC was due to XO-induced superoxide generation, neonatal piglets were pretreated with allopurinol (an XO inhibitor) and then subjected to global hypoxia and reoxygenation. The results of this study actually showed a 2-fold worsening of histological intestinal injury score at 48 hours after hypoxia, indicating that mechanisms of I-R other than XO-induced superoxide release may be responsible for the intestinal injury, increased permeability, and bacterial translocation which are thought to be involved in NNEC.[d]

Pharmacologic therapy to prevent these deleterious leukocyte–endothelial cell interactions in susceptible tissues would be aimed at inhibiting the accumulation of pro-inflammatory mediators, altering neutrophil activation, or attenuating integrin expression. In a mouse model of ischemia/reperfusion injury, a potent neutrophil inhibitor (PR 39) decreased leukocyte rolling and adherence in ischemic mesentery, and also decreased myocardial PMN accumulation.[24] More current research into the pathogenesis of intestinal I-R injury and NNEC has revealed that PAF plays a role in gut barrier dysfunction and the development of NNEC.[25,26] In a rat intestinal I-R model, pretreatment with the PAF antagonist lexipafant prevented intestinal albumin leakage and bacterial translocation.[26] In various models of myocardial I-R, these PAF antagonists have been shown to protect against reperfusion injury, and have even passed safety and efficacy trials in humans. Evidence suggests that myocardial injury in these models is due to the release of inflammatory mediators such as PAF, thromboxanes, leukotrienes, and endothelins released during ischemia and distributed throughout the heart during reperfusion.[27]

Lidocaine: Pharmacology

Lidocaine (Xylocaine)[e] is a local anesthetic with muscle relaxant and weak antihistaminic properties.[28] Lidocaine is currently used in veterinary and human medicine as a local anesthetic, and for the treatment of ventricular dysrhythmias associated with blunt

cardiac trauma, myocardial ischemia, and cardiac surgery.[28] The most common adverse effects reported are dose related (serum level) and mild. Central nervous system signs include drowsiness, depression, ataxia, muscle tremors, nausea, and vomiting (usually transient). Adverse cardiac effects are usually associated with PR and QRS interval prolongation and QT interval shortening. Lidocaine may increase ventricular rates if used in patients with atrial fibrillation. If an IV bolus is given too rapidly, hypotension may occur; however, this is usually limited to high plasma concentrations.[29]

Local anesthetics commonly used in veterinary medicine are classified into 2 groups (amino-esters or amino-amides), depending on the link between an aromatic molecule and their tertiary amine. Amino-amide local anesthetics such as lidocaine, mepivacaine,[f] and bupivacaine[g] all share this amide linkage. The amino-esters are metabolized into *p*-aminobenzoic acid, which causes allergies in human patients. This does not occur with the amino-amides.[30] All local anesthetics including lidocaine inhibit the propagation of nerve impulses by binding to Na^+ channel receptor sites in the nerve membrane, thereby slowing the rate of depolarization and preventing propagation of action potentials. More specifically, in the heart, lidocaine is classified as a class 1B (membrane stabilizing) antiarrhythmic agent, which is distinguished by its ability to reduce the rate of phase 0 depolarization and conduction velocity in injured cardiac cells. It does so by binding to fast Na^+ channels, while having a minimal effect on action potential duration, and refractory period compared to class 1A drugs.[30] This effect of lidocaine to bind to Na^+ channels is important in relation to its ability to prevent I-R injury in the heart and brain.

Pharmacokinetics

Lidocaine is not effective orally as it has a high first-pass effect. If very high oral doses are given, toxic symptoms occur (due to active metabolites) before therapeutic levels can be reached. Following a therapeutic IV bolus dose, the onset of action is generally within 2 minutes and the duration of action is 10–20 minutes.[29] If a constant infusion is begun without an initial IV bolus, it may take up to an hour for therapeutic levels to be reached. Intramuscular injections may be given every 1.5 hours in the dog, but because monitoring and adjusting dosages are difficult, it should be reserved for cases where IV infusions are not possible.

After injection, lidocaine is rapidly distributed from the plasma into highly perfused organs (kidney, liver, lungs, heart) and is distributed widely throughout body tissues and into milk. It has a high affinity for fat and adipose tissue, and is bound to plasma proteins, primarily α_1-acid glycoprotein.[27] Lidocaine binding to this protein is highly variable and concentration dependent in the dog and may be higher in dogs with inflammatory disease.[29] The volume of distribution (V_d) is 4.5 L/kg in the dog. Lidocaine is rapidly metabolized in the liver to active metabolites (mono ethylglyclyxlyidide (MEGX) and glyclyxlyidide (GX)). The terminal half-life of lidocaine in humans is 1.5–2 hours and has been reported to be 0.9 hours in the dog.[29] The half-lives of lidocaine and MEGX may be prolonged in patients with cardiac failure or hepatic disease. Less than 10% of a parenteral dose is excreted unchanged in the urine.[29]

Lidocaine and I-R Injury

Recently, experiments in various animal models of ischemia and reperfusion injury have yielded more specific biochemical information relating to the ability of lidocaine to prevent ROS formation and lipid peroxidation. Possible mechanisms of these actions for lidocaine include (1) inhibition of Na^+/Ca^{2+} exchange and Ca^{2+} accumulation during ischemia, (2) scavenging of hydroxyl radical, (3) decreased release of superoxide from granulocytes, and (4) decreased PMN activation, migration into ischemic tissues, and subsequent endothelial dysfunction (Figure 2). The following information will outline the scientific evidence that lidocaine indeed does work by these 4 mechanisms. Lidocaine, when used in various shock states, may help prevent the formation of ROS and therefore decrease tissue lipid peroxidation, cell death, and development of MODS.

Current published human information: In human medicine, lidocaine has traditionally been used as the agent of choice for suppression of ventricular tachycardia and fibrillation after cardioversion. Its use in human medicine is justified due to its low incidence of toxicity and high degree of antiarrhythmic effect.[2,8] More recently, most likely due to concurrent studies on its antioxidant properties, intravenous IV lidocaine has been used to prevent reperfusion injury-associated dysrhythmias, which may occur after thrombolysis for myocardial infarction.[31] In the GUSTO-I and GUSTO-IIb clinical trials, the use of prophylactic IV lidocaine caused a statistically significant decrease in death rate at 24 hours, and revealed a trend toward lower in-hospital mortality and death at 30 days.[31] Intravenous lidocaine has also been studied in clinical trials for its ability to prevent reperfusion dysrhythmias after

coronary bypass and aortic cross-clamp. In the control group, the incidence of reperfusion ventricular fibrillation after coronary bypass was 70%, which was reduced to 11% in the lidocaine-treated group. The authors attributed a higher cardiac output in the treated group to a lower incidence of reperfusion dysrhythmias.[32] Furthermore, in another clinical study,[33] lidocaine combined with adenosine was shown to reduce infarct size in patients with myocardial infarction.

The most recent human studies have been *in vitro* studies that attempt to demonstrate lidocaine's antioxidant and anti-inflammatory effects on PMNs. It has been theorized that much of the myocardial necrosis that occurs after cardiac repair, and subsequent reperfusion is mediated by ROS formation and subsequent PMN infiltration.[34] In these *in vitro* studies, PMNs are stimulated to secrete superoxide, which can then be measured by photometric techniques. In 2 different studies, lidocaine suppressed the superoxide production by activated PMNs as measured by chemiluminescence.[35,36] In another study involving PAF-primed PMNs, local anesthetics in the same class as, and including lidocaine inhibited superoxide radical production at clinically relevant concentrations.[37]

Lidocaine also markedly inhibited the chemiluminescence of XO enzyme, which indicates that it may also inhibit XO, and thereby the production of superoxide during reperfusion.[37] Although lidocaine has been used prophylactically to prevent dysrhythmias related to myocardial infarction, its use in human trauma medicine for the treatment of other conditions that cause reperfusion injury, SIRS, and MODS is anecdotal at best. At a major university trauma center,[38] lidocaine was given along with other antioxidants to patients admitted to the ICU for varying shock states and other septic conditions. Although no randomized study was performed and other antioxidants were administered, the authors selected lidocaine in these patients, because of a body of scientific evidence that they referenced in their review article, demonstrating the ability of lidocaine to inhibit PLA_2, block the production of tumor necrosis factor (TNF), PAF and subsequent PMN activation, and inhibition of cytokine release from PMNs.[38]

Veterinary and animal model studies: There are no clinical experiments involving the prophylactic use of lidocaine to prevent reperfusion injury in dogs and cats. Recently, however, there has been an increasing amount of anecdotal discussion involving the use of lidocaine in the treatment of head trauma[h] and to prevent reperfusion injury associated with GDV.[i] This anecdotal use of lidocaine most likely stems from the large body of evidence in animal models, which demonstrates its ROS scavenging and anti-inflammatory properties. In published experiments, lidocaine is theorized to ameliorate the negative effects of ROS, prevent tissue lipid peroxidation, and subsequent end organ damage by the following mechanisms: (1) Na^+/Ca^{2+} exchange inhibition; (2) ROS scavenging of both superoxide and hydroxyl radical resulting in cytoprotection; and (3) prevention of deleterious leukocyte–endothelial cell interactions (see Figure 2 for a summary of these mechanisms).

Lidocaine and Na^+/Ca^{2+} Exchange Inhibition

Recent animal experimentation has been conducted to study the ability of lidocaine (and other related compounds) to limit Na^+/Ca^{2+} loading in various tissues. Various models of myocardial reperfusion injury have shown that pretreatment of ischemic tissues with lidocaine and other Na^+/Ca^{2+} exchange inhibitors reduces the formation of ventricular dysrhythmias and infarct size.[39,40] It was theorized that decreased Na^+ and Ca^{2+} accumulation in cardiac tissue was at least, in part, responsible for these beneficial effects.

In various rat models of myocardial ischemia/reperfusion, preischemiac treatment with lidocaine resulted in (1) enhancement of postischemic contractile recovery, (2) a decrease in ventricular dysrhythmias, (3) suppression of tissue Na^+, K^+, Ca^{2+}, and Mg^{2+} accumulation, and (4) attenuation of the release of creatine kinase and ATP metabolites in a dose-dependent manner.[39,40] In an experiment using various antiarrhythmic agents, lidocaine suppressed the V_{max} value of the rat left ventricular muscle cell (a marker of Na^+ channel blockade) in a dose-dependent manner.[41] The degree of postischemic contractile recovery seen in the presence of lidocaine and other antiarrhythmic agents was inversely related to tissue Na^+ and Ca^{2+} accumulation after reperfusion. This suggests that the class I antiarrhythmic agents in this study inhibit Na^+ overload in ischemic/reperfused myocardial cells.[41] In another model of myocardial ischemia/reperfusion injury, R56865 (a Na^+/Ca^{2+} exchange inhibitor) was administered to guinea pigs. When given even during reperfusion, R56865 delayed sustained fibrillation and improved ionic homeostatis in myocardial cells.[42] In a similar experiment, lidocaine was administered 5 minutes before the induction of global ischemia/reperfusion and resulted in a significantly decreased incidence of ventricular fibrillation and tachycardia, with a concomitant decrease in Na^+ and Ca^{2+} accumulation.[43] Another novel Na^+/Ca^{2+} inhibitor, KB-R7943, inhibited Na^+/Ca^{2+} exchange in cardiac sarcolemmar reticular vesicles in the canine heart.[42] Lidocaine showed a similar

beneficial effect to this novel drug on pretreatment recovery of ischemic myocardium.[44]

Lidocaine has also been shown to protect neuronal tissue from ischemic damage by similar mechanisms. Current theories of brain ischemia/reperfusion injury include release of intracellular Ca^{2+} and neurotoxic chemicals such as glutamate, which then promote ROS generation from neuronal tissue.[12] In the ischemic gerbil hippocampus, preischemic administration of lidocaine delayed the onset of ischemia-induced membrane depolarization and inhibited the release of intracellular Ca^{2+}, thereby protecting neurons from histological evidence of ischemia. This effect of lidocaine was presumably related to inhibiting the release of Ca^{2+} from intracellular stores and by inhibiting its influx from the extracellular space.[45] In similar rat models of brain ischemia, lidocaine was shown to inhibit increases of cytosolic Ca^{2+} and intracellular glutamate, both having been implicated in causing release of ROS molecules and subsequent neuronal cell death. Administration of IV lidocaine before reperfusion in various I-R models (1) reduced Na^+ and Ca^{2+} release from mitochondria,[46] (2) suppressed glutamate accumulation in hippocampal and cortical tissue,[47] (3) prevented histological damage to hippocampal slices without blocking action potentials,[48] and (4) reduced infarct size, improved neurologic outcome and body weight.[49]

The reduction of cellular depolarization, Na^+ and Ca^{2+} loading during ischemia may explain the neuroprotective action of lidocaine in these *in vitro* studies and also in animal models. Increased intracellular Ca^{2+} in ischemic neuronal tissue is postulated to activate phospholipases, which leads to the dissolution of lipid membranes and the subsequent release of free fatty acids and arachidonic acid (AA) metabolites.[12] These AA metabolites (prostaglandins, leukotrienes, thromboxanes, PAF) and more ROS generation lead to increased vascular permeability, PMN activation, and initiate local vascular endothelial injury.[12] It is possible that lidocaine, if given before reperfusion in ischemic neuronal tissue, may stop cellular Ca^{2+} accumulation and ameliorate injury.

Furthermore, since cytosolic Ca^{2+} has been theorized to be necessary as a co-factor for the conversion of XD to XO (Figure 1), it is possible that the phenomenon of Ca^{2+} exchange inhibition by lidocaine causes a decrease in the formation of superoxide radicals through the preservation of myocardial and neuronal XD. As previously discussed, lidocaine has been shown to inhibit markedly the chemiluminescence of the XO enzyme.[37] Therefore, the use of lidocaine as a stabilizing treatment during shock may prevent injury to the heart and brain during the reperfusion period, through the preservation of XD and a concomitant decrease in superoxide radical formation. *In vivo* experiments evaluating the effect of lidocaine on XO-induced superoxide production are needed in order to define fully this potentially valuable antioxidant effect.

ROS and lidocaine-induced cytoprotection

Lidocaine may be involved in mechanisms of reperfusion injury other than inhibition of Na^+/Ca^{2+} exchange through the blocking of Na^+ channels and subsequent reduction of superoxide radical formation. As previously discussed, numerous experiments in both gastric and cardiac models of reperfusion injury have implicated hydroxyl radical formation and generation of superoxide from neutrophils as potent mediators of lipid peroxidation and cell death (Figure 1).

Previous studies of experimentally induced GDV have shown that lidocaine reliably reduced gastric and cardiac histopathologic and ultrastructural tissue damage and arrhythmias[j] caused by decreased tissue perfusion. Specifically, IV bolus infusion of 2.2 mg/kg lidocaine, followed by constant rate infusion of 66 μg/kg/min to 5 dogs before decompression in a similar experimental GDV model reduced gastric and cardiac ultrastructural cell damage by 40%.[50,51] It was postulated that the decreased mitochondrial swelling and cardiac myocyte injury in lidocaine-treated subjects, which was demonstrated on transmission electron microscopy, was due to its ability to protect mitochondrial oxidative phosphorylation and decreased membrane permeability.[50,51] In a small pilot study carried out by the author, the use of perioperative lidocaine in dogs with clinical GDV reduced the formation of multifocal ventricular dysrhythmias from 75% in untreated animals to 18% in those receiving lidocaine before decompression.[k] Since it is postulated that ROS formation and PMN infiltration are responsible for the myocardial injury and subsequent dysrhythmias that occur in GDV patients,[9,15] it is possible that administration of lidocaine before reperfusion ameliorates this injury in both experimental and clinical settings. Recent experiments have demonstrated that lidocaine is an effective hydroxyl radical scavenger, while also decreasing superoxide release from granulocytes (Figure 2). Experiments involving rat lung ischemia/reperfusion demonstrate that lidocaine significantly attenuates injury, while decreasing the formation of cyclooxygenase products, which are downstream markers of lipid peroxidation.[52] Recently, experimental techniques (such as electron spin resonance) that detect ROS through the use of compounds called 'spin trapping agents' have been optimized. Large magnets are used to detect the suspected radical in blood or

tissues, attached to the spin trapping agent. In a landmark electron spin resonance experiment, lidocaine was proven to inhibit the formation of a hydroxyl radical adduct linked to a 'spin trapping agent' in a dose-dependent manner.[53] Lidocaine also caused a dose-dependent inhibition of NADPH-dependent lipid peroxidation when bovine lung microsomes were incubated with NADPH in the presence of Fe(3+)-ADP.[53] Furthermore, in a rabbit model of 30-minute myocardial ischemia and 48 hours of reperfusion (a similar time frame as GDV patients), pretreatment with lidocaine reduced infarct size by 50% compared with controls. This reduction also significantly decreased tissue PMN infiltration and superoxide production by rabbit neutrophils.[54] In similar experiments by the same author, performed to clarify the effect of lidocaine on PMN functions, lidocaine caused a reduction of infarct size in the rabbit myocardium, inhibition of PMN infiltration and hemorrhage and decreased PMN chemiluminescence.[55] Specifically, the effects of lidocaine on PMN activation in whole blood were measured by chemiluminescence. A significant reduction in the chemiluminescence response to the chemoattractant FMLP was obtained with rabbit and human blood, when pretreated with lidocaine.[55] This study demonstrates the profound effect that lidocaine had on neutrophil function. Other *in vivo* studies in 3 different species (rabbit, pig, human) have shown that lidocaine inhibited superoxide production and suppressed the respiratory burst in PMNs.[54,56,57] Lidocaine was also shown to inhibit phagocytosis and subsequent superoxide and H_2O_2 production in RAW 264.7 macrophages.[58] Furthermore, when lidocaine was compared to bretylium tosylate in a porcine model of myocardial ischemia/reperfusion injury, it significantly decreased myocardial infarct size, while also reducing the *in vitro* release of superoxide from porcine granulocytes.[56] In a model of canine brain I-R injury for only 60 minutes of reperfusion, dogs pretreated with lidocaine showed a significant decrease in malondialdehyde concentration, but no decrease in PMN activation.[59] One hour of reperfusion, however, may not have been a long enough time period to observe significant suppression of the respiratory burst by lidocaine.

It is clear from these experiments that lidocaine protects organs from ROS injury via scavenging of the hydroxyl radical and decreasing production of superoxide from granulocytes of certain species. Further research should be performed in order to more clearly elucidate the biochemical mechanisms by which lidocaine inhibits ROS formation and subsequent myocardial, gastric and neuronal reperfusion injury.

Lidocaine and endothelial dysfunction

Once ROS have been generated, their presence in ischemic tissues begins a vicious cycle of PMN activation and expression of PMN chemoattractants and inflammatory cytokines leading to even more neutrophil infiltration of ischemic tissues. Accumulation of activated PMNs in ischemic tissue leads to physical disruption of the endothelial and epithelial barriers, widening of endothelial and epithelial intracellular tight junctions, increase in tissue permeability (caused by lipid peroxidation), and cell death.

Lidocaine has been shown to reduce the release of these inflammatory cytokines (PAF, PLA_2, IL-6, IL-8) from macrophages and PMNs. It has also been shown to reduce PMN adhesion to endothelial surfaces *in vivo*, and inhibits upregulation of PMN CD11/CD18 *in vitro*. In a model of canine allograft transplantation, lidocaine was added to the donor flush and given to the recipient at thoracotomy. Compared to controls, dogs receiving lidocaine had a significantly decreased bronchoalveolar lavage PMN count and allograft myeloperoxidase activity, indicating that less PMN activation had occurred. Furthermore, in lidocaine-treated animals, PMN CD11b expression was maintained at basal levels 2 hours post-reperfusion.[60] In another model of rabbit lung injury, lidocaine pretreatment reduced superoxide production, PMN infiltration, and IL-6 and IL-8 levels in lung tissue exposed to hydrochloric acid.[61] Furthermore, lidocaine has been shown in *in vitro* studies to inhibit chemoattractant-induced superoxide release and FMLP(formyl-methionyl-leucyl-phenylalanine)-induced CD11 upregulation in a dose-dependent manner.[62] In a more recent experiment, lidocaine and other local anesthetics also inhibited adhesion, phagocytosis, and the production of superoxide radical and hydrogen peroxide in rat neutrophils that were isolated by peritoneal lavage after stimulation with glycogen.[63] With regard to sepsis, lidocaine significantly inhibited leukocyte–endothelial cell adhesion and macromolecular leakage in rat postcapillary venules, suggesting that the drug may have a role in preventing endothelial damage in sepsis,[64] which occurs frequently in traumatized dogs and cats. In order to ascertain the role of lidocaine as an inhibitor of PLA_2 in acute respiratory distress syndrome, the drug was administered to rabbits before induction of acute lung injury. Pretreatment with lidocaine attenuated the amount of histopathologic lung injury, the amount of PMN accumulation, and decreased the peripheral neutrophil and platelet counts.[65]

Application to human/veterinary emergency and critical care: Intravenous lidocaine, if administered before reperfusion, prevents Na^+/Ca^{2+} accumulation,

Table 1: Lidocaine – potential therapeutic effects

Therapeutic/clinical effect	Relevance to reperfusion injury
Sodium channel blocker – local anesthetic/antiarrhythmic	Decreased Na^+/Ca^{2+} exchange
Calcium channel blocker – antiarrhythmic	Decreased xanthine oxidase activity
Decreased neuronal excitotoxicity/ glutamate release	Decreased secondary brain injury
Hydroxyl radical scavenger – anti-inflammatory	Decreased lipid peroxidation
Inhibits neutrophil functions – anti-inflammatory	Decreased superoxide release
Inhibits cytokine release – anti-inflammatory	Decreased endothelial dysfunction

decreases neuronal excitotoxicity, decreases the formation of ROS (superoxide, hydroxyl radical), and prevents ROS-induced PMN infiltration, cytokine-induced PMN adhesion, and endothelial dysfunction in both *in vivo* and *in vitro* models (see Table 1 for a summary of therapeutic effects). Although it has already been shown that prophylactic lidocaine administration prevents reperfusion dysrhythmias and myocardial infarction in humans, its uses in other causes of hypovolemia, hypoperfusion, and sepsis are less clear. Although our veterinary patients rarely experience myocardial infarction, they are subject to other diseases (cerebral and spinal cord trauma, hypovolemic shock, GDV, cardiac and pulmonary contusions, strangulating intestinal obstruction) in which ischemia and reperfusion injury are likely to initiate ROS formation. The prophylactic use of lidocaine in these situations may prevent ROS-induced lipid peroxidation and the systemic inflammatory response that ensues. As shown in experimental models of sepsis and endotoxemia, lidocaine may also decrease the endothelial dysfunction caused by the release and activation of inflammatory mediators (PLA_2, TNF, PAF, IL-6, IL-8). Since PLA_2 activation has also been shown to induce TNF-α and subsequent PMN activation,[66] it is possible that lidocaine acts to decrease neutrophil chemotaxis and adhesion and subsequent ROS formation by this 'two-hit' mechanism of cytokine reduction (Figure 2).[38] Increased serum secretory PLA_2 has been shown in clinical trials to be linked to MODS.[67] For many years in veterinary medicine, glucocorticosteroids have been used in shock situations in an attempt to modify inflammation and the SIRS response. Since a major action of these corticosteroids in shock is to inhibit PLA_2,[68] it is clear that further clinical trials should be performed, especially to ascertain the role of lidocaine in PLA_2 inhibition, TNF-α secretion, and subsequent endothelial dysfunction. With the current controversy in both human and veterinary medicine over the use of glucocorticosteroids in disease states that cause SIRS, due to their apparent gastrointestinal and endocrine side effects, the substitution of IV lidocaine for the glucocorticoids may give clinicians an effective and safe treatment alternative.

Conclusions and recommendations for future studies: In summary, in experimental models, administration of lidocaine before significant reperfusion decreases ROS formation, neutrophil activation, chemotaxis, and the ensuing lipid peroxidation that occurs in vital organs (heart, lung, brain, intestine) during reperfusion. Controlled clinical trials involving lidocaine and its use in actual diseases and syndromes (head and spinal cord trauma, GDV, equine strangulating obstruction, hypovolemic/septic shock, respiratory distress, endotoxemia) are needed in both human and veterinary medicine. Specifically, *in vivo* experiments involving lidocaine's effect on XO-induced superoxide production are needed in order to elucidate this valuable potential antioxidant effect. In clinical settings, blocking the influx of intracellular and cytosolic Ca^{2+} by lidocaine administration may decrease lipid peroxidation via decreased superoxide radical production, not only in the heart but also in other organs (intestine, lung, brain), where it has been proven that this pathway causes significant lipid peroxidation and organ damage. For life-threatening conditions such as GDV and equine intestinal strangulating obstruction, experimental studies such as those discussed above should be repeated with lidocaine, with specific emphasis on its hydroxyl radical and superoxide scavenging abilities as well as survival, morbidity, and mortality. Furthermore, well-designed clinical experiments involving perioperative use of lidocaine in the canine and equine patient should be performed to see what effect it would have on morbidity and mortality. In summary, it is clear from these experiments that clinical trials involving lidocaine therapy for cerebral and other organ ischemia are needed in dogs, cats, and horses in order to ascertain if these cytoprotective effects are evident in trauma patients. With the paucity of therapies that are either safe or effective, the use of lidocaine may become an attractive alternative in emergency medicine's arsenal of therapies for hemodynamically unstable patients in which MODS contributes to their morbidity and mortality.

Footnotes

[a] Gfeller, 2000, Veterinary Information Network and Gfeller, 1999, Veterinary Information Network

[b] Foltz, 2002, Veterinary Information Network and Gfeller, 2000, Veterinary Information Network
[c] Desferal, Novartis AG, Basel, Switzerland
[d] Cassutto BH, Ozolek JA, Argyle JC, et al. Effect of allopurinol on hypoxic/hypothermic intestinal injury in the neonatal piglet (abstract). Conference of Military Perinatology Research at Aspen, 1997
[e] Xylocaine, AstraZeneca Pharmaceuticals, Wilmington, DE
[f] Carbocaine, Sanofi-Synthelabo, New York, NY
[g] Marcain, AstraZeneca Pharmaceuticals, Wilmington, DE
[h] Gfeller, 2000, Veterinary Information Network and Gfeller, 1999, Veterinary Information Network
[i] Foltz, 2002, Veterinary Information Network and Gfeller, 2000, Veterinary Information Network
[j] Keith JC, personal communication
[k] Cassutto BH, Benson BW, Keith JC. Prevention of ventricular dysrhythmias in canine gastric dilatation volvulus through the use of peri-operative intravenous lidocaine therapy (abstract). 7th Annual International Veterinary Emergency and Critical Care Symposium, Orlando, 6–10 September 2000

References

1. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia–reperfusion injury. Anesthesiology 2001; 94:1133–1138.
2. Rochat MC. An introduction to reperfusion injury. Compend Contin Educ Pract Vet 1991; 13(6):923–930.
3. Yamazaki S, Fujibayashi Y, Rajagopalan RE, et al. Effects of staged versus sudden reperfusion after acute coronary artery occlusion in the dog. J Am Coll Cardiol 1986; 7:564–572.
4. Winquist RJ, Kerr S. Cerebral ischemia–reperfusion injury and adhesion. Neurology 1997; 49:S23–S26.
5. Kong SE, Blennerhassett LR, Heel KA, et al. Ischaemia–reperfusion injury to the intestine. Aust NZ J Surg 1998; 68:554–561.
6. Brady CA, Otto CM. Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction. Vet Clin North Am Small Anim Pract 2001; 31(6):1147–1162, v–vi.
7. Olanders K, Zhengwu S, Borjesson A, et al. The effect of intestinal ischemia and reperfusion injury on ICAM-1 expression, endothelial barrier function, neutrophil tissue influx and protease inhibitor levels in rats. Shock 2000; 18(1):86–92.
8. Liu XL, Nozari A, Basu S, et al. Neurologic outcome after experimental cardiopulmonary resuscitation: a result of delayed and potentially treatable neuronal injury. Acta Anaesthesiol Scand 2001; 46(5):537–546.
9. Badylak SF, Lantz GC, Jeffries M. Treatment of reperfusion injury in dogs with surgically-induced gastric-dilatation-volvulus. Am J Vet Res 1992; 53:1594–1598.
10. Moore RM, Muir WW, Granger DN. Mechanisms of gastrointestinal ischemia–reperfusion injury and potential therapeutic interventions: a review and its implications in the horse. J Vet Intern Med 1995; 9(3):115–132.
11. Cassutto BH, Misra HP, Pfeiffer CJ. Intestinal post ischemic reperfusion injury: studies with neonatal necrotizing enterocolitis. Acta Physiologica Hungarica 1989; 72(1–3):363–369.
12. Leonard SE, Kirby R. The role of glutamate, calcium and magnesium in secondary brain injury. J Vet Emerg Crit Care 2002; 12(10):17–32.
13. Davis S, Helfaer MA, Traytsman RJ, et al. Parallel antioxidant and antiexcitotic therapy improves outcome after incomplete global cerebral ischemia in dogs. Stroke 1997; 28(1):198–204.
14. Matsuda T, Arakawa N, Takuma K, et al. SEA0400, a novel and selective inhibitor of the Na^+–Ca^{2+} exchanger, attenuates reperfusion injury in the *in vitro* and *in vivo* cerebral ischemic models. J Pharmacol Exp Ther 2001; 298(1):249–256.
15. Lantz GC, Badylak SF, Hiles MC, et al. Treatment of reperfusion injury in dogs with experimentally-induced gastric-dilatation-volvulus. Am J Vet Res 1992; 53:1594–1598.
16. Smart SC, Sagar KB, Warltier DC. Differential roles of myocardial Ca^{2+} channels and Na^+/Ca^{2+} exchange in myocardial reperfusion injury in open chest dogs: relative roles during ischemia and reperfusion. Cardiovasc Res 1997; 36(3):337–346.
17. Segawa D, Sjoquist PO, Wang QD, et al. Calcium antagonist protects the myocardium from reperfusion injury by interfering with mechanisms directly related to reperfusion: an experimental study with the ultrashort-acting calcium antagonist clevidipine. J Cardiovasc Pharmacol 2000; 36(3):338–343.
18. Yamuda K, Matsui K, Satoh K, et al. Reduction of myocardial infarct size by SM-20550, a novel Na(+)/H(+) exchange inhibitor, in rabbits. Eur J Pharmacol 2000; 404(1–2):201–212.
19. Nakamura A, Harada K, Sugimoto H, et al. Effects of KB-R7943, a novel Na^+/Ca^{2+} exchange inhibitor, on myocardial ischemia/reperfusion injury. Nippon Yakurigaku Zassi 1998; 111(2):105–115.
20. Horne MM, Pascoe PJ, Ducharme NG. Attempt to modify reperfusion injury of equine jejunal mucosa using dimethylsulfoxide, allopurinol and intraluminal oxygen. Vet Surg 1994; 23(4):241–249.
21. Vatistas NJ, Snyder JR, Hildebrand SV, et al. Effects of U-74398G, a novel 21-aminosteroid, on small intestinal ischemia and reperfusion injury in horses. Am J Vet Res 1996; 57(5):762–770.
22. Moore RM, Bertone AL, Bailey MQ, et al. Neutrophil accumulation in the large colon of horses during low-flow ischemia and reperfusion. Am J Vet Res 1994; 55(10): 1454–1463.
23. Cassutto BH, Pfeiffer CJ, Misra HP. Role of active oxygen species in hypothermia induced intestinal injury in weanling hamsters. Fed Proc 1987; (6):2047.
24. Hoffmeyer MR, Scalia R, Ross CR, et al. PR-39, a potent neutrophil inhibitor, attenuates myocardial ischemia–reperfusion injury in mice. Am J Physiol Heart Circ Physiol 2000; 279(6):H2824–H2828.
25. Ewer K. Role of platelet-activating factor in the pathophysiology of necrotizing enterocolitis. Acta Paediatr Suppl 2002; 91(437):2–5.

26. Sun Z, Wang X, Deng X, et al. Beneficial effects of lexipafant, a PAF antagonist on gut barrier dysfunction caused by intestinal ischemia and reperfusion in rats. Dig Surg 2000; 17(1):57–65.
27. Loucks EB, Symersky P, Qayumi AK. Platelet-activating factor antagonism: a new concept in the management of regional myocardial ischemia–reperfusion injury. J Invest Surg 1997; 10(6):321–328.
28. Hondeghem LC, Roden DM. Agents used in cardiac arrhythmias, In: Katzung BG. ed. Basic and Clinical Pharmacology. New York: Lange Medical Books/ McGraw-Hill; 1998. pp. 232–233.
29. Plumb DC. Lidocaine HCl, In: Veterinary Drug Handbook, Pocket Edition. Ames: Iowa State Press; 2002. p. 504.
30. Adams HR Antiarrhythmic agents, In: Adams HR. ed. Veterinary Pharmacology and Therapeutics. Ames: Iowa State Press; 1995. pp. 358–371.
31. Alexander JH, Granger CB, Sadeowski Z, et al. Prophylactic lidocaine use in acute myocardial infarction: incidence and outcomes from two international trials. The GUSTO-I and GUSTO-IIb investigators. Am Heart J 1999; 137(5):799–805.
32. Baraka A, Kawkabani N, Dabbous A, et al. Lidocaine for prevention of reperfusion ventricular fibrillation after release of aortic cross-clamping. J Cardiothorac Vasc Anesth 2000; 14(5):531–533.
33. Garratt KN, Holmes DR, Moloina-Viamonte V, et al. Intravenous adenosine and lidocaine in patients with acute myocardial infarction. Am Heart J 1998; 136(2):196–204.
34. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res 2002; 53(1):31–47.
35. Hollman MW, Gross A, Jelacin N, et al. Local anesthetic effects on priming and activation of human neutrophils. Anesthesiology 2001; 95(1):113–122.
36. Arakawa K, Takahashi H, Nakagawa S, et al. The effects of lidocaine on superoxide production and p47 Phox translocation in opsonized zymosan-activated neutrophils. Anesth Analg 2001; 93(6):1501–1506.
37. Gunyadin B, Demiryurek AT. Interaction of lidocaine with reactive oxygen and nitrogen species. Eur J Anaesthesiol 2001; 18(12):816–822.
38. Kirton OC, Civetta JM. Ischemia–reperfusion injury in the critically ill: a progenitor of multiple organ failure. Crit Care Med 1999; 7(1):87–95.
39. Kamiyam T, Tanonaka K, Harada H, et al. Mexiteline and lidocaine reduce post-ischemic and biochemical dysfunction of perfused hearts. Eur J Pharmacol 1995; 272(2–3): 151–158.
40. Van Emous JG, Nederhoff MG, Ruigrok TJ, et al. The role of the Na^+ channel in the accumulation of intracellular Na^+ during myocardial ischemia: consequences for post-ischemic recovery. J Mol Cell Cardiol 1997; 29(1):85–96.
41. Takeo S, Tanonaka K, Hayashi M, et al. A possible involvement of sodium channel blockade of class-I-type antiarrhythmic agents in post-ischemic contractile recovery of isolated, perfused hearts. J Pharmacol Exp Ther 1995; 273(3):1403–1409.
42. Scheufler E, Mozes A, Guttman I, et al. R56865 is antifibrillatory in reperfused ischemic guinea pig hearts, even when given only during reperfusion. Cardiovasc Drugs Ther 1995; 9(4):545–553.
43. Tosaki A, Balint S, Szekeres L. Protective effect of lidocaine against ischemia and reperfusion-induced arrhythmias and shifts of myocardial sodium, potassium, and calcium content. J Cardiovasc Pharmacol 1998; 12(6):621–628.
44. Nakamura A, Harada K, Sugimoto H, et al. Effects of KB-R7943, a novel Na^+/Ca^{2+} exchange inhibitor, on myocardial ischemia/reperfusion injury. Nippon Yakurigaku Zassi 1998; 111(2):105–115.
45. Liu K, Adachi N, Yanase H, et al. Lidocaine suppresses the anoxic depolarization and reduces the increase in the intracellular Ca^{2+} concentration in gerbil hippocampal neurons. Anesthesiology 1997; 87(6):1470–1478.
46. Terada H, Ohta S, Nishikawa T, et al. The effect of intravenous or subarachnoid lidocaine on glutamate accumulation during transient forebrain ischemia in rats. Anesth Analg 1999; 89(4):957–961.
47. Zhang Y, Lipton P. Cytosolic Ca^{2+} changes during *in vitro* ischemia in rat hippocampal slices: major roles for glutamate and Na^+-dependent release from mitochondria. J Neurosci 1999; 19(1):3307–3315.
48. Taylor CP, Burke SP, Weber ML. Hippocampal slices: glutamate overflow and cellular damage from ischemia are reduced by sodium-channel blockade. J Neurosci Meth 1995; 59(1):121–128.
49. Lei B, Cotrell JE, Kass IS. Neuroprotective effect of low-dose lidocaine in a rat model of transient focal cerebral ischemia. Anesthesiology 2001; 95(2):445–451.
50. Pfeiffer CJ, Keith JC, Cho CH, et al. Gastric and cardiac organoprotection by lidocaine. Acta Physiologica Hungarica 1989; 73(2–3):129–136.
51. Pfeiffer CJ, Keith JC, April M. Topographic localization of gastric lesions and key role of plasma bicarbonate concentration in dogs with experimentally induced gastric dilatation. Am J Vet Res 1987; 48:262–267.
52. Das KC, Misra HP. Amelioration of postischemic reperfusion injury by antiarrhythmic drugs in isolated perfused rat lungs. Environ Health Perspect 1994; 102(10):117–121.
53. Das KC, Misra HP. Antiarrhythmic agents- Scavengers of hydroxyl radicals and inhibitors of NADPH-dependent lipid peroxidation in bovine lung microsomes. J Biol Chem 1992; 267(27):19172–19178.
54. Vitola JV, Forman MB, Holsinger JP, et al. Reduction of myocardial infarct size in rabbits and inhibition of activation of rabbit and human neutrophils by lidocaine. Am Heart J 1997; 133(3):315–322.
55. Vitola JV, Forman MB, Holsinger JP, et al. Inhibition of neutrophil function by lidocaine as a mechanism for the beneficial effect to reduce myocardial reperfusion injury. J Am Coll Cardiol 1995; 25(2, suppl 1):102A–103A.
56. Hatori N, Roberts RL, Tadokoro H, et al. Differences in infarct size with lidocaine as compared with bretylium

tosylate in acute myocardial ischemia and reperfusion in pigs. J Cardiovasc Pharmacol 1991; 18(4):581–588.
57. Hyvonnen PM, Kowolik MJ. Dose dependent suppression of the neutrophil respiratory burst by lidocaine. Acta Anaesthiol Scand 1998; 42(5):565–569.
58. Das KC, Misra HP. Impairment of raw 264.7 macrophage function by antiarrhythmic drugs. Mol Cell Biochem 1994; 132:151–162.
59. Lantos J, Roth E, Temes G. Effects of lidocaine on cerebral lipid peroxidation and neutrophil activation following complete compression ischemia. Arch Int Pharmacodyn Ther 1996; 331(2):179–188.
60. Schmid RA, Yamashita M, Ando K, et al. Lidocaine reduces reperfusion injury and neutrophil migration in canine lung allografts. Ann Thoracic Surg 1996; 61(3):;949–955.
61. Nishina K, Mikawa K, Takao Y, et al. Intravenous lidocaine attenuates acute lung injury induced by hydrochloric acid aspiration in rabbits. Anesthesiology 1998; 88(5):1300–1309.
62. Ohsaka A, Saionji K, Sato N, et al. Local anesthetic lidocaine inhibits the effect of granulocyte colony stimulating factor on human neutrophil functions. Exp Hematol 1994; 22(5):460–466.
63. Azuma Y, Shinohara M, Wang P, et al. Comparison of inhibitory effects of local anesthetics on immune functions of neutrophils. Int J Immunopharmacol 2000; 22(10):789–796.
64. Schmidt W, Schmidt H, Bauer H, et al. Influence of lidocaine on endotoxin-induced leukocyte–endothelial cell adhesion and macromolecular leakage *in vivo*. Anesthesiology 1997; 87(3):617–624.
65. Kiyonari Y, Nishina K, Mikawa K, et al. Lidocaine attenuates acute lung injury induced by a combination of phospholipase A2 and trypsin. Crit Care Med 2000; 28(2):484–489.
66. Yan GT, Hao XH, Li ZJ. Tumor necrosis factor induced enhancement of neutrophil chemotaxis and adhesion through mediating of phospholipase A2 activation. Sheng Li Hsueh Poa 1995; 47(6):544–550.
67. Patrick DA, Moore EE, Silliman CC, et al. Secretory phospholipase A_2 activity correlates with postinjury multiple organ failure. Crit Care Med 2001; 29(5): 989–993.
68. Goldfien A. Adrenocorticosteroids and adrenocortical antagonists, In: Katzung BG. ed. Basic and Clinical Pharmacology. New York: Lange Medical Books/McGraw-Hill; 1998. p. 639.

Erratum

The recognition and treatment of the intermediate syndrome of organophosphate poisoning in a dog. K. Hopper, J. Aldrich and S.C. Haskins. J Vet Emer Crit Care 2002; 12(2):99–103.

A letter regarding this article was published in the March 2003 issue of the journal. The credentials of J. Aldrich were given as DVM, DACVECC, DACVA, however, DACVECC and DACVA were included erroneously. The journal apologizes for this error.