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In vitro analysed effects of two different in vivo administered lidocaine dosages on the equine jejunal smooth muscle challenged by an ischemia-reperfusion-injury-model (IRIM)

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Summary

Lidocaine as a prokinetic drug is acting dose-dependently on the ischemia-reperfusion (IR) injured equine jejunal smooth muscle. The aim of the study was to examine the effects of different dosages of lidocaine on jejunal smooth muscle contractility in vitro as a basic research approach to examine the potential mechanism of lidocaine. Sustainability of this in vivo effect of applied lidocaine was tested under in vitro conditions. Hypothesis: Application of a higher initial dose of lidocaine during IR in vivo could change, improve or even impair the contractility effects on jejunal smooth muscle in vitro. 12 horses received either a 1.3 mg/kg (IRL1; N = 7) or 2.6 mg/kg (IRL2; N = 5) lidocaine bolus infusion over 10 minutes followed by 0.05 mg/kg/min intravenously for 5 minutes while artificial IR injury on the jejunum was induced. To examine the effects of lidocaine on jejunal smooth muscle function, isometric force performance (amplitude, frequency and contractility) was measured in vitro at two different times (t1,t2). The influence of either in vitro lidocaine supplementation (KHB+L) or no supplementation (KHB) was studied to assess the sustainability of lidocaine effects. IRL2 KHB+L showed a significant higher frequency of contraction at t2 compared to IRL1KHB+L. Amplitude of contractions and contractility were significantly decreased in the IRL1 KHB tissues compared to IRL1 KHB+L at t2. The IRL2 KHB tissues at t2 showed a significant decrease of frequency and amplitude of contractions compared to the IRL2 KHB+L. There was a significant decrease in frequency and an increase in amplitude of contractions and in contractility in IRL 1 KHB+L from t1 to t2. In IRL1 KHB a significant decrease in frequency was observed but increase in amplitude of contractions and contractility was lacking from t1 to t2. IRL2 KHB expressed a significant decrease in frequency and a significant increase in amplitude from t1 to t2, while amplitude, frequency and contractility in IRL2 KHB+L were not influenced by time. High dosage lidocaine bolus infusion with further supplementation increased frequency of contractions and maintained amplitude of contractions over the experimental time. This in vitro study suggested that immediate application of a high bolus dosage may improve protective effects of lidocaine furthermore in vitro. At the moment, no pharmacokinetic data for a 2.6 mg/kg over 10 min. lidocaine bolus in vivo is available. Recommending a higher initial lidocaine bolus in vivo, especially because of negative side effects, requires further investigation.

Keywords: lidocaine / equine jejunum / contractility / smooth muscle / prokinetic effects / anesthesiology / horse

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In vitro untersuchte Effekte von zwei unterschiedlichen in vivo verabreichten Lidokaindosierungen auf die glatte Muskulatur des equinen Jejunums in einem Ischämie-Reperfusions-Modell

Lidokain wirkt dosisabhängig prokinetisch auf die Ischämie-Reperfusion (IR) geschädigte glatte Muskulatur des equinen Jejunums. Ziel dieser Studie war, die Effekte unterschiedlicher Lidokaindosierungen in vivo auf die Kontraktilität der glatten Muskulatur des equinen Jejunums in vitro zu untersuchen. Dieser experimentelle Grundlagenansatz soll zum Verständnis möglicher Wirkungsmechanismen von Lidokain beitragen. Zusätzlich wurde die Nachhaltigkeit der in vivo ausgelösten Effekte unter in vitro Bedingungen überprüft. Hypothese: Die Applikation eines hohen initialen Lidokainbolus in vivo während der IR könnte die Kontraktilität der glatten Muskulatur des Jejunums in vitro verändern, verbessern oder sogar negativ beeinflussen. Während eines artifiziell induzierten Ischämie-Reperfusionsschadens des Jejunums erhielten 12 Pferde entweder eine 1,3 mg/kg (IRL1; N = 7) oder 2,6 mg/kg (IRL2; N = 5) Lidokainbolusinfusion über 10 Minuten gefolgt von einer Erhaltungsdosis von 0,05 mg/kg/min i.v. über 5 Minuten. Um den Effekt von Lidokain auf die glatte Muskulatur des Jejunums zu untersuchen wurde die isometrische Kontraktionskraft (Amplitude, Frequenz und Kontraktilität) in vitro an zwei verschiedenen Zeitpunkten (t1, t2) beurteilt. Der Einfluss einer weiteren Lidokainsupplementation in vitro (KHB+L) oder keiner weiteren Supplementation (KHB) wurde evaluiert, um die Nachhaltigkeit des Lidokaineffekts zu überprüfen. Die Kontraktionsfrequenz der IRL2 KHB+L war im Vergleich zur IRL1KHB+L signifikant höher zum Zeitpunkt t2. Die Amplitude der Kontraktion und die Kontraktilität der glatten Muskulatur des Jejunums waren bei der IRL1 KHB zum Zeitpunkt t2 im Vergleich zur IRL1 KHB+L signifikant reduziert. Die IRL2 KHB zeigte zum Zeitpunkt t2 im Vergleich zur IRL2 KHB+L eine signifikant verminderte Frequenz und Amplitude der Kontraktion. Innerhalb der IRL1 KHB+L konnte eine signifikante Abnahme der Frequenz sowie ein Anstieg der Amplitude und der Kontraktilität zwischen t1 und t2 festgestellt werden. Die IRL1 KHB zeigte ebenfalls im Vergleich von t1 zu t2 einen Abfall der Kontraktionsfrequenz, ein Anstieg der Kontraktionsamplitude und der Kontraktilität konnte nicht festgestellt werden. Die IRL2 KHB zeigte einen signifikanten Frequenzabfall und einen Amplitudenanstieg im Vergleich zwischen t1 und t2 während bei der IRL2 KHB+L keine Veränderungen von Amplitude, Frequenz und Kontraktilität über die Zeit festgestellt werden konnten. Die höher dosierte Lidokainbolusinfusion mit zusätzlicher Zugabe von Lidokain in vitro erzielte eine stetigere Kontraktilität der glatten Muskulatur im Vergleich zur niedriger dosierten Bolusinfusion. Diese In vitro-Studie deutet darauf hin, dass die Applikation eines hoch dosierten Bolus die protektiven Effekte von Lidokain noch weiter verbessern kann. Da zu diesem Zeitpunkt keine pharmakokinetischen Daten für einen Lidokainbolus von 2,6 mg/kg über 10 Minuten verfügbar sind, bedarf der Vorschlag eines höheren Lidokainbolus in vivo vor allem wegen der möglichen unerwünschten Arzneimittelwirkungen weiterer Untersuchung.

Schlüsselwörter: Lidokain / equines Jejunum / Kontraktilität / glatte Muskulatur / prokinetische Effekte / Anästhesie / Pferd

Introduction

Lidocaine, an amide-type local anaesthetic, is used for various purposes in veterinary medicine. Besides its local anesthetic effects, lidocaine is used for antiarrhythmic and antiepileptic treatment (*Löscher* et al. 2003). Furthermore, lidocaine is known to have protective and/or prokinetic effects on intestinal smooth muscle (*Nieto* et al. 2000, *Guschlbauer* et al. 2010a) and heart muscle (*Takeo* et al. 1989) after ischemia-reperfusion (IR) injury although the mechanism of its protective and prokinetic effects are still unclear. Administration of lidocaine significantly decrease liberation of substances from body cells such as hypoxia-induced release of creatine kinase from the intestinal smooth muscle (*Guschlbauer* et al. 2010a) and from the heart muscle (*Takeo* et al. 1989), and attenuates inflammatory response by decreasing the plasma concentrations of complement factors and pro-inflammatory cytokines released by inflammatory cells (*Herroeder* et al. 2007).

Previous studies revealed that in vitro lidocaine supplementation of 25 x 10^9 ng/ml = 25 mg/L = 10^{-4} mol/L is needed to improve effectively contractile activity of the equine jejunal smooth muscle (*Guschlbauer* et al. 2010a, *Nieto* et al. 2000). After continuous infusion of lidocaine as used in the treatment of post operative ileus (POI) (bolus of 1.3 mg/kg over 10 min. followed by continuous rate infusion (CRI) of 0.05 mg/kg) plasma lidocaine concentrations increased up to approximately 1000 ng/ml after 3 hours and remained stable at approximately 950 ng/ml over a 96 hour infusion period (*van Hoogmoed* et al. 2004, *Navas de Solis* and *McKenzie III* 2007, *Dickey* et al. 2008). Only approximately one-tenth of these plasma concentrations (Mean ± standard error of the mean (SEM) 97.2±17.7 ng/ml, n = 12) were achieved after an in vivo lidocaine bolus of 1.3 mg/kg over 10 min. followed by 0.05 mg/kg over 5 min. during the ischemic period of an IRIM. Lidocaine tissue concentrations in jejunal smooth muscle achieved 133.9±24.5 ng/mg tissue wet weight measured directly after resection (*Guschlbauer* et al. 2011). Lack of lidocaine pharmacokinetics in healthy and IRIM horses causes difficulties in extrapolation of in vitro effective lidocaine concentrations of organ bath buffers into in vivo effective CRI concentrations.

Recent in vitro studies were performed with isolated circular smooth muscle of distal equine jejunum to determine the influence of lidocaine on smooth muscle contractility. Experiments were performed in healthy and artificially IR challenged jejunal smooth muscle, demonstrating that intestinal smooth muscle contractility responded dose-dependently to lidocaine supplementation in vitro and that IR-injured smooth muscle is more susceptible to lidocaine (*Guschlbauer* et al. 2010a, 2011). Lidocaine was able to restore contractility of IR-injured smooth muscle to the level of healthy smooth muscle, indicating a repair mechanism (*Guschlbauer* et al. 2010a). The in vivo application of lidocaine (1.3 mg/kg IV bolus followed by 0.05 mg/kg/min IV as a continuous infusion) during artificial IR increased contractility and frequency of contractions in vitro compared to untreated IR-injured smooth jejunal muscle. Hence lidocaine is also able to prevent smooth muscle injury provoked by artificial IR. When additional in vitro lidocaine supplementation was performed after in vivo application, contractility could further be improved (*Guschlbauer* et al. 2011). However, very high dosages of lidocaine in vitro reduce contractile performance of smooth muscle (decreasing in vitro contractility after supplementing 100-400 mg/l) indicating an accumulation within the muscle cell (*Guschlbauer* et al. 2010a).

Based on the latter results of the recent in vitro studies, it was hypothesised that the short-term application of a higher initial dose of lidocaine during IR in vivo could change, improve or even impair the contractility effects on jejunal smooth muscle in vitro. To test the effects of a higher dosage on smooth muscle contractility in vitro, artificially IR-injured tissues of horses infused with two different lidocaine dosages in vivo were analyzed for basic contractility and for their responsiveness to additionally supplemented lidocaine in vitro. Furthermore, sustainability of these effects was tested.

Material and Methods

Animals

Twelve adult horses randomly divided into two groups were used in this study. The first group (IRL1: ischemic and reperfused, with in vivo lidocaine infusion dose 1 = 1.3 mg/kg/10 min. IV followed by 0.05 mg/kg/5 min. IV) consists of six mares and one gelding (N = 7). Six of these horses with a mean age of 13.4 years were warmblood horses and one was a Thoroughbred. The second group (IRL2: ischemic and reperfused, with in vivo lidocaine infusion dose 2 = 2.6 mg/kg/10 min. IV followed by 0.05 mg/kg/5 min. IV) with a mean age of 15.6 years included one gelding, one stallion and three mares (N = 5). Three horses were warmblood horses, one horse was a Standardbred and one a Thoroughbred. All horses were healthy and showed no gastrointestinal disorders. Horses were kept on hay and water ad libitum two weeks prior to surgery.

Surgical procedure of ischemia-reperfusion injury

Following general anesthesia and ventral laparotomy in dorsal recumbency all horses underwent an IRIM as described previously (*Guschlbauer* et al. 2010a, 2011). All animal procedures were approved by the State Office for Consumer Protection and Food Safety in accordance with the German Animal Welfare Law.

In vivo lidocaine infusion protocol

Directly after ligation of the mesenteric vessels and luminal closure (ischemia), infusion of lidocaine using a 2 % commercially available solution (Lidocaine, bela pharm, Vechta, Germany) was commenced. Horses in the IRL1-group received a loading bolus infusion lasting 10 minutes (1.3 mg/kg IV) followed by a CRI of 0.05 mg/kg/min IV for 5 minutes. The IRL2-group received a higher loading bolus infusion lasting 10 minutes (2.6 mg/kg IV) followed by a CRI of 0.05 mg/kg/min IV for the remaining 5 minutes of the ischemic period.

Tissue preparation

Immediately after resection the segment was divided into 2 parts. One part (KHB: Krebs-Henseleit-Buffer without lidocai-

ne supplementation, 4 muscle strips/horse, nIRL1 = 28, nIRL2 = 20) was transferred into a modified Krebs-Henseleit-Buffer (in mmol/L: 117.0 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgCl_2$, 1.2 NaH_2PO_4, 25.0 $NaHCO^3$, 11.0 glucose, gassed with 95% O_2 and 5% CO_2 (pH 7.4, 38°C)). The other part of the resected jejunal segment was transferred into Krebs-Henseleit-Buffer which was supplemented with 25 mg/L lidocaine (KHB+L: Krebs-Henseleit-Buffer with lidocaine supplementation 25 mg/L, 8 muscle strips/horse, nIRL1 = 56, nIRL2 = 40). This dosage was set to be optimal effective by preliminary in vitro studies which showed a dose-dependent response of in vitro measured contractility to lidocaine reaching "steady-state" at lidocaine concentrations ranging between 20 and 100 mg/L (*Guschlbauer* et al. 2010a). Tissue was prepared as previously described by (*Guschlbauer* et al. 2010a, 2011). Briefly, strips of the circular smooth muscle of equal size and weight were prepared from each horse of IRL1 and IRL2 and mounted into the force measurement apparatus fitted with isometric force transducers. Eight KHB+L strips (n = 8) were prepared per horse and mounted into an organ bath filled with 10 ml KHB + 25 mg/L lidocaine. Furthermore, four KHB strips (n = 4) were prepared per horse and were mounted in organ baths without supplementation of lidocaine. The initial tension of all muscle strips was adjusted to 2 g, because preliminary studies showed that 2 g of tension resulted in optimal muscle length for maximal isometric force development in the jejunum (*Nieto* et al. 2000). To study the effects of lidocaine on smooth muscle cells and interstitial cells of Cajal (ICC) only, the tissue strips in the organ bath were treated with tetrodotoxin (TTX 1 mol/L) in order to deactivate the enteric nervous system neurons. A successful inhibition was validated by lack of response to electric field stimulation (*Boddy* et al. 2004).

Measurement of basal contractile activity

After equilibration (acclimatization to the in vitro conditions of the smooth muscle strips over 30 minutes) the basal contractility (= contractility after deactivation of the enteric nervous system with TTX) was recorded for 205 minutes. With TTX treated equine jejunal muscle strips show spontaneous contractions (basal contractility) mediated by the electric pacemaker function of ICCs (*Takaki* 2003, *Fintl* et al. 2004) without any neuronal participation. These spontaneous contractions can be defined by amplitude (isometric force of contraction, mN) and by frequency (peaks/min). By use of these 2 variables, the area under the curve (AUC) for all contractions within one minute (contractility, mN/min) was calculated. Amplitude, frequency of contractions and contractility were analyzed at minute 10-25 (t1) and minute 65-80 (t2) after equilibration. Contractions of smooth muscle samples were digitalized with a chart recorder (4.8 kHz/DC) and data were collected digitally (Spider 8 chart recorder and Catman Easy software, version 1.01, HBM).

Statistical analysis

Data were given as means ± SEM of N = 7 in IRL1 and N = 5 in IRL2. Significance of difference of basal contractility, frequency of contractions and amplitude was statistically tested between IRL1 and IRL2 with unpaired Student´s t test. When comparing contractility, frequency and amplitude within one group (IRL1 or IRL2) but at different times (t1 or t2) or different buffer containing (KHB or KHB+L) paired Student`s t-test was used for statistical analysis (graphpad.prism, version 4.0, GraphPad Software Inc). The level of statistic significance (p) was set at $p < 0.05$(*), $p < 0.01$ (**), $p < 0.001$ (***).

Results

Effects of different lidocaine dosages applied in vivo on contractility of jejunal smooth muscle in vitro

To assess the only effect of the higher lidocaine bolus dosage contractile performance of IRL1 and IRL2 intestinal smooth muscle at either t1 or t2 were compared. This was done for KHB+L muscle strips and for KHB strips separately. The mean frequency of contractions, amplitude and contractility did not differ between IRL1 and IRL2 tissue at t1 and t2 with one exception, the significant higher frequency ($p < 0,01$) in the KHB+L tissue of IRL2 group at t2 (7,0±0,75 peaks/min, n IRL2 KHB+L = 40, N = 5) compared to KHB+L of IRL1 at t2 (3,9±0,62 peaks/min, n IRL1 KHB+L = 56, N = 7).

Effects of in vitro lidocaine supplementation on contractility of jejunal smooth muscle in vitro

To assess the effect of lidocaine supplementation after resection of the intestinal segments KBH and KBH+L muscle strips at each time point t1 and t2 were compared for IRL1 and IRL2 separately regarding their contractile performance. At t1 the IRL1 and IRL2 tissue showed no significant differences in frequency, amplitude and contractility, when different buffer conditions were used (KHB or KHB+L). However, at t2 amplitude of contractions and contractility were significantly decreased in the IRL1 KHB tissues compared to IRL1 KHB+L muscle strips. The mean frequency of contractions did not show any differences between IRL1 KHB and IRL1 KHB+L at t2. The IRL2 KHB tissues at t2 showed a significant decrease of frequency and amplitude of contractions compared to the IRL2 KHB+L muscle strips. However, these changes in IRL2 KHB did not result in a significant change of contractility (Figure 1).

Effect of time on contractility of jejunal smooth muscle in vitro

To assess the effect of time in in vivo lidocaine treated tissues changes of IRL1 and IRL2 from t1 to t2 were analyzed for each buffer condition (KHB, KHB+L) separately. There is a significant decrease in frequency and an increase in amplitude of contractions as well as in contractility in IRL1 KHB+L from t1 to t2. In IRL1 KHB a similar significant decrease in frequency was observed but increase in amplitude of contractions and contractility was lacking from t1 to t2. In IRL2 KHB+L no changes of frequency, force and contractility over the time were observed. In contrast, IRL2 KHB expressed a decrease in frequency and a slight, but significant increase in amplitude. However, contractility of IRL2 KHB was not influenced by time. There was no significant difference of contractility between IRL1 t2 KHB-L and IRL2 t2 KHB-L, and IRL1 t1 KHB-L and IRL1 t1 KHB-L (Figure 1).

Discussion

The present study presents a sequel study to the basic research approaches by *Nieto* et al. 2000 and *Guschlbauer* et al. 2010a to improve the knowledge on lidocaine prokinetic effects in intestinal smooth muscle of horses. The present results are proving the hypothesis that a higher initial dose of lidocaine during IR in vivo could change and slightly improve but not impair the contractility of jejunal smooth muscle in vitro. The in vivo applied dosages of 1.3 and 2.6 mg/kg body weight over 10 minutes did result in only slight differences in contractile performance irrespectively of additive lidocaine supplemented to the smooth muscle samples during the initial period of the in vitro experiment. Only frequency of contractions was significantly enhanced over time in IRL2 samples supplemented with lidocaine additively. This indicates a small positive effect of the doubled lidocaine dosage on smooth muscle and also interstitial cells of Cajal (ICC) function. Protection of ICC may have ameliorated the frequency of contractions (*Engelking* et al. 1987). We hypothesised that doubling the in vivo dosage led to lidocaine accumulation and provoked associated protective effects in tissues within the steady state phase observed in vitro. A steady state phase of lidocaine effect was observed in former in vitro experiments using IR-injured jejunal smooth muscle (*Guschlbauer* 2010a). Furthermore, a slight improvement was also observed regarding the in vitro contractile performance of IRL2 samples supplemented with lidocaine additively which was maintained steadier over time compared to the IRL1 KHB+L samples. The previously described wash-out effect of lidocaine during in vitro incubation was reflected by the lower contractile activity for IRL1 KHB and IRL2 KHB muscle strips at t2 compared to t1. Hence sustainability of the effects of lidocaine can only be maintained by continuous application of lidocaine.

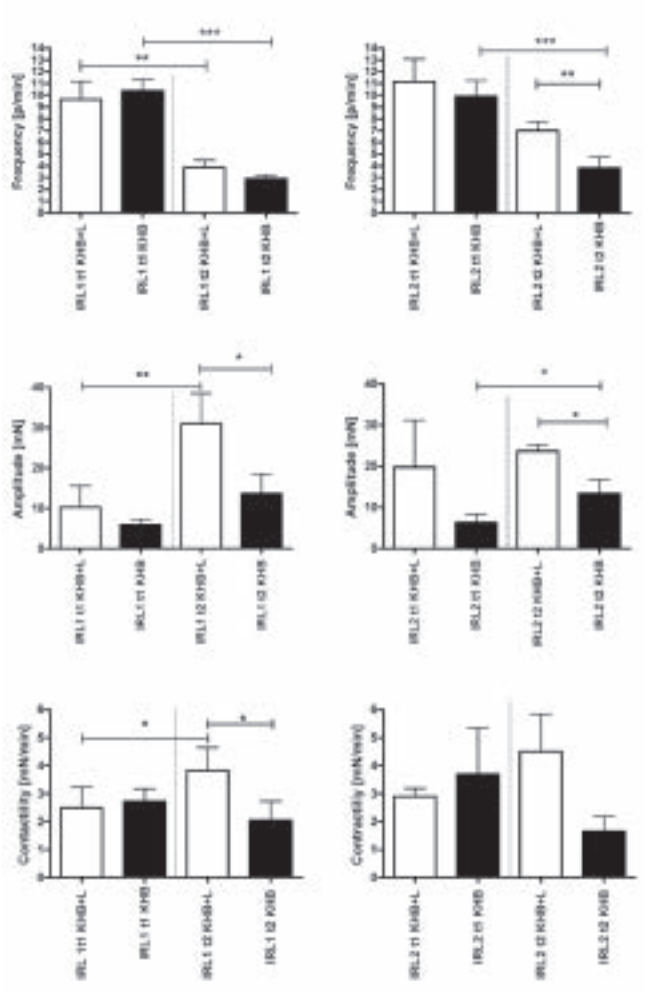

Fig. 1 Comparison of in vitro contractile activity (parameters frequency, amplitude, contractility) between IRL1 (left side) and IRL2 (right side) at different time points (t1, t2) and different organ bath solutions {KHB+L (□), KHB (■)}. Bars represents means ± SEM ($n_{IRL1\ KHB} = 28$, $n_{IRL1\ KHB+L} = 56$, $n_{IRL2\ KHB} = 20$, $n_{IRL2\ KHB+L} = 40$). Significance levels are *p <0.05, **p <0.01, ***p <0.001.
*Vergleich der kontraktilen Aktivität (Parameter: Frequenz, Amplitude, Kontraktilität) zwischen IRL1 (links) und IRL2 (rechts) in vitro an unterschiedlichen Zeitpunkten (t1, t2) und mit verschiedenen Pufferzusammensetzungen {KHB+L (□), KHB (■)}. Säulen geben Mittelwerte ± SEM ($n_{IRL1\ KHB} = 28$, $n_{IRL1\ KHB+L} = 56$, $n_{IRL2\ KHB} = 20$, $n_{IRL2\ KHB+L} = 40$) an. Signifikanzniveaus bei *p <0.05, **p <0.01, ***p <0.001.*

A limitation of this study is the time of IR-injury. Because this study is a sequel to *Guschlbauer* et al. (2010a, 2011), an IR of the intestinal wall of 15 min was chosen to impair smooth muscle contractility in vitro efficiently as it was determined by former studies. However, this short-term IR appear not to damage the intestinal wall macroscopically but histologically. Signs of cell damage such as edema were observed in a former study by *Guschlbauer* et al. (2010b). It should be clear that IR-time should be longer to extrapolate these results into a clinical background.

Addressing the question what relevance these experiments may have for clinical treatment of POI, it has to be taken into account that the supplementation of 25 mg/L lidocaine in the KHB in vitro is much higher than measured effective serum concentrations (about 980 ng/ml) in vivo by IV lidocaine infusion. However, the same dosage of lidocaine (10^{-4} mmol/L) used in this experiment was also described as effective dose in vitro by *Nieto* et al. (2000). This discrepancy between in vivo and in vitro effective dosages might be based on certain biochemical features of lidocaine but cannot be explained satisfactorily yet. What we know so far is that pharmacokinetics of lidocaine in the horse are influenced by many factors such as general anesthesia or withholding of food (*Fintl* et al. 2010, *Feary* et al. 2005). Accumulation in the smooth muscle tissue could also account for the observed differences in effective dosages and has already been suggested (*Guschlbauer* et al. 2011).

Summary and Conclusion

An initial lidocaine bolus of 2.6 mg/kg applied IV during IR-injury slightly ameliorates smooth muscle contractile performance in vitro, but only when additive lidocaine is continuously supplemented to avoid a "wash out" over time. Pharmacokinetic studies are necessary to evaluate the body distribution of lidocaine and to assess the effective tissue lidocaine concentrations. The role of tissue lidocaine accumulation and its dynamic changes during lidocaine infusion should be elucidated to convey information about the cellular mechanisms of lidocaine´s prokinetic effect. It should be clear that before recommending a higher lidocaine bolus in vivo for POI treatment further investigations are needed especially for: pharmacokinetic data for a higher (2.6 mg/kg/10 min.) lido-

cainebolus administered in vivo, the discrepancy between in vivo and in vitro lidocaine concentrations and intracellular and extracellular biochemics for lidocaine acting on the equine jejunal smooth muscle.

Conflict of interest statement

None of the authors has any financial or personal relationship that could inappropriately influence or bias the content of the paper.

Animal welfare statement

All animal procedures were approved by the State Office for Consumer Protection and Foof safety in accordance with the German Animal Welfare Law. Registration number: 33.12-42502-04-07/1398.

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