

Cardiovascular, respiratory, gastrointestinal and behavioral effects of intravenous lidocaine in healthy, conscious horses and evaluation of the relationship with lidocaine and monoethylglycinexylidide serum concentrations

Cardiovasculaire, respiratoire, gastro-intestinale en gedragseffecten van intraveneuze lidocaïne-toediening bij gezonde paarden bij bewustzijn en evaluatie van de relatie met serumconcentraties van lidocaïne en mono-ethylglycinexylidide

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ABSTRACT

This study aimed to evaluate the relationship between the serum concentrations of lidocaine/monoethylglycinexylidide (MEGX) and their effects on several systems in horses. Five healthy, conscious horses received a two-hour placebo intravenous infusion followed by a two-hour lidocaine infusion (bolus of 1.3 mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min). Lidocaine and MEGX serum concentrations were sampled every ten to fifteen minutes during the experiment, and the presence of muscle fasciculations and loss of balance as well as the respiratory, digestive and cardiovascular systems of the five horses were evaluated by means of different non-invasive methods. During the lidocaine infusion, the mean (\pm SD) lidocaine and MEGX concentrations were respectively 768.88 ± 93.32 ng/ml and 163.08 ± 108.98 ng/ml. The infusion of lidocaine significantly influenced the presence of fasciculations, caused a statistically but non-clinically significant decrease of systolic and diastolic blood pressures, which were both correlated with lidocaine and MEGX serum concentrations, and it increased the duodenal contractions frequency, which was correlated with the serum lidocaine concentration. In this study, mild hypotensive and prokinetic effects of short-term lidocaine infusion were observed.

SAMENVATTING

Deze studie had als doel de relatie te bepalen tussen de serumconcentraties van lidocaïne/monoethylglycinexylidide (MEGX) en hun effect op de verschillende lichamelijke stelsels bij het paard. Vijf gezonde paarden bij bewustzijn kregen een twee uur durende placebo-intraveneuze infusie gevolgd door een twee uur durende lidocaïne-infusie (bolus van 1,3 mg/kg in tien minuten gevolgd door een constante infusie van 0,05 mg/kg/min). De lidocaïne- en MEGX-serumconcentraties werden om de tien à vijftien minuten gemeten. Het evenwichtsverlies, de spiertrillingen, het ademhalings-, spijsverterings- en cardiovasculaire stelsel werden beoordeeld met behulp van verschillende niet-invasieve methoden. Tijdens de toediening van de lidocaïne-infusie was de gemiddelde (\pm standaarddeviatie) lidocaïne- en MEGX-concentratie respectievelijk $768,88 \pm 93,32$ ng/ml en $163,08 \pm 108,98$ ng/ml. De toediening van een lidocaïne-infusie beïnvloedde significant de aanwezigheid van trillen. Ook veroorzaakte ze een statistisch maar niet-klinisch significante afname van de systolische en diastolische bloeddruk, die beide correleerden met de lidocaïne- en MEGX-serumconcentratie. Verder verhoogde ze eveneens de duodenale contractiefrequentie, die correleerde met de serumlidocaïne-concentratie. In de voorliggende studie werden milde hypotensieve en prokinetische kortetermijneffecten van een lidocaïne-infusie waargenomen.

INTRODUCTION

Intravenous lidocaine is frequently used in horses in different medical conditions. In cardiac pathologies, it is used as an antiarrhythmic drug to treat ventricular tachycardia (McGuirk and Muir, 1985). It has analgesic properties (Murrell et al., 2005; Robertson et al., 2005) and its systemic administration decreases the anesthetic requirements of inhalant agents (Doherty and Frazier, 1998). It is also commonly used in horses with digestive problems, to treat and prevent ileus and gastrointestinal pain in the postoperative period or in horses with small intestine inflammatory disease (Brianceau et al., 2002; Malone et al., 2006; Torfs et al., 2009), and to improve mucosal repair after ischemic intestinal injury (Cook et al., 2008). Lidocaine treatment has been associated with enhanced short-term survival of horses after colic surgery (Torfs et al., 2009).

The dosage of intravenous lidocaine commonly used in horses is a bolus of 1.3mg/kg (usually administered over 5-15 minutes) followed by a continuous rate infusion (CRI) of 0.05mg/kg/minute, as recommended by Malone et al., (1998).

When administered intravenously, lidocaine has been associated with several side effects, mainly affecting the central nervous, musculoskeletal and cardiovascular systems.

Eye blinking, anxiety, mild sedation, muscle fasciculation, ataxia and collapse are the most commonly reported signs of toxicity in clinical use in horses (Brianceau et al., 2002; Malone et al., 2006; Meyer et al., 2001).

Lidocaine is metabolized by the liver and is transformed by the cytochrome P450 system in monoethylglycinexylidide (MEGX), which is further metabolized to glycinexylidide (GX) and 4-hydroxy-2,6-xylidine (Oellerich et al., 1987). The adverse reactions related to the use of continuous intravenous lidocaine have been attributed in some cases to the accumulation of lidocaine or its principal metabolites MEGX and GX (Strong et al., 1973) and are usually associated with a too high infusion rate leading to a lidocaine serum concentration higher than the target therapeutic range of 1–2 mg/dL (Meyer et al., 2001; Brianceau et al., 2002; Malone et al., 2006). Clinically, lidocaine side effects usually respond rapidly to discontinuation or slowing of the infusion rate. There is no evidence of structural damage to nerve fibers or cells after lidocaine toxicity in other species (Richie and Greene, 1990).

The pharmacokinetics of lidocaine and its metabolites have been described in healthy, conscious horses (Dickey et al., 2008) and in healthy (Milligan et al., 2006) or colic horses (Navas de Solís and McKenzie III, 2007) after laparotomy, but the relationship between lidocaine or its metabolites concentrations and their pharmacologic effects has not been described in depth. Several studies have been conducted in con-

scious and healthy horses in order to evaluate the effect of a specific dosage of intravenous lidocaine on somatic and visceral nociception (Robertson et al., 2005), on cardiac electrical activity and blood pressure (Meyer et al., 2001) or on gastrointestinal motility (Milligan et al., 2007; Rusiecki et al., 2008).

The aim of the present study was to evaluate the effects of an infusion of lidocaine and to determine the correlations between the serum concentrations of lidocaine/MEGX and their effects on the behavior and the respiratory, cardiovascular and gastrointestinal systems of healthy horses during an infusion of lidocaine at the dosage commonly used in clinical cases.

MATERIAL AND METHODS

This study was approved by the Ethical Committee of the University of Liège (number 385).

Animals

Five warmblood horses (four mares and one gelding) were used in the study. Their weight ranged from 418 to 497 kg (mean \pm SD: 493 \pm 92,6 kg) and their age ranged from 11 to 22 years (mean \pm SD: 16,4 \pm 5,8 years). All horses were clinically healthy based on the history and on an in-depth clinical examination.

The horses were kept in stall with straw bedding. They had access to hay and water ad libitum excepted the twelve hours preceding the protocol, when they were fasted using a muzzle without restriction of water. The day before the protocol, the abdominal region of the animals was clipped. During the protocol, the horses had no access to water and food.

Study design

Each horse was evaluated during a two-hour intravenous infusion of a placebo (NaCl 0.9%, Baxter – Viaflo, Belgium) followed by a two-hour intravenous infusion of lidocaine (Xylocaine 2%, Astra Zeneca, Belgium).

Protocol

The experiment was carried out in the morning for every horse. Within one hour before starting the protocol, a 14-gauge polytetrafluoroethylene catheter (Catheter 14G Intraflon 2, Vygon, France) was placed aseptically into both the left and right jugular veins. The skin at the area of the catheter placement was not anesthetized with lidocaine in order to avoid interference with the subsequent measurements of lidocaine and MEGX. The catheter in the left jugular vein was used for administration of the infusions, and the catheter in the right jugular vein was used to collect the blood samplings.

The infusion of lidocaine was performed at the

usual clinical dosage and consisted of a single intravenous bolus of 1.3 mg/kg of lidocaine administered over 10 minutes followed by a CRI of 0.05 mg/kg/min during 110 minutes (Malone et al., 1998). One volume of commercial lidocaine 2%² (20 mg/ml) was added to four volumes of saline in order to obtain a concentration of 4 mg/ml solution of lidocaine. The infusion of placebo consisted of the administration of NaCl 0.9% at the same rate as the lidocaine infusion.

The rate of administration of both fluids was controlled by use of an intravenous fluid administration pump (Flo-Gard 6200, Baxter, Belgium).

Timing of the investigations

The following times (Tminutes) were defined: T0 (prior to lidocaine or placebo administration) and T10, T15, T30, T45, T60, T75, T90, T105 and T120 (minutes following the beginning of the lidocaine or placebo administration). The continuously evaluated parameters were classified in periods finishing at the corresponding T time (for example: T30 corresponds to the period beginning just after T15 and ending at T30).

Behavioral evaluation

The presence of muscle fasciculations and loss of balance was recorded throughout the experiment and was scored as 0 (absence) or 1 (presence) for the corresponding time period.

Respiratory evaluation

The respiratory rate was obtained by feeling the expiratory airflow with a hand placed near the external nare and watching the horse's nostril movements during one minute at each time point (McGorum and Dixon, 2007).

Cardiovascular evaluation

Heart rate and electrocardiographic (ECG) analysis

For each horse, an ECG was recorded continuously from 15 minutes preceding the start of the infusion (lidocaine or placebo) until the end of the infusion by using a Holter system (System Holter Vista, Novacor, France). Data were retrospectively blindly analyzed after their transfer on a computer. The presence of arrhythmias was evaluated by visual inspection of the ECG tracings and controlled by an ECG analyzer program (HolterSoft Ultima 2.5.5, Novacor 2001-2009, France). The heart rate was calculated by visual inspection of the ECG tracing (number of QRS complexes) during the last minute of each time period. The type and the frequency of the possible cardiac arrhythmias were recorded and attributed to the corresponding T time.

Systemic arterial blood pressure

Systolic and diastolic systemic arterial blood pressures were collected using a non-invasive oscillometric system (Digital blood pressure monitor KH 8088, Kompennass, Germany). The inflatable cuff for the blood pressure measurement had a length of 25 cm and a width of 5.5 cm. It was positioned at the base of the tail and centered over the coccygeal artery. For each time point, the systolic and diastolic arterial pressures were obtained by calculating the mean of three consecutive measurements (Parry et al., 1980).

Gastrointestinal evaluation

Gut sounds

Gut sounds were evaluated by auscultation of the left flank during one minute for each time point and recorded as the number of peristaltic sounds heard over one minute.

Duodenal ultrasonography

The duodenum was examined by transabdominal ultrasonography (Aloka SSD 900, Aloka Holding Europe AG, Switzerland) in the middle third (dorso-ventrally) of the abdomen between the fourteenth and seventeenth right intercostal spaces just ventral to the right kidney and dorsal or dorsolateral to the cecal base, as described by Kirberger et al. (1995). Appropriate contact between the ultrasonographic probe (Convex transducer UST 990-3.5 MHz, Aloka Holding Europe AG, Switzerland) and the skin was provided by the previous clipping of the hair and a contact gel applied directly on the skin at the time of the examination. The ultrasonographic images of the duodenum during the last three minutes of each T period were recorded on a videotape for later blind evaluation. Subsequently, the recording was used to obtain the frequency of the duodenal contractions and the duodenal wall thickness, which was measured when the intestine was fully open. The frequency of the contractions of the duodenum was calculated using the entire recording for each T period. The value of the duodenal wall thickness was obtained by the mean of three measurements, which were taken from the hyperechoic outer serosal surface to the inner hyperechoic mucosal surface (Figure 1).

Blood sampling and laboratory methods

At each T time, a 5-ml blood sample was collected from the right jugular catheter and placed into a plain vacuum tube (Vacuette 9 ml Z Serum Clot activator, Greiner Bio-One GmbH, Austria). The blood sample was allowed to clot before being centrifuged (Centrifuge EBA 200S, Hettich, Germany) at 4000 rpm for ten minutes at room temperature. The serum was then

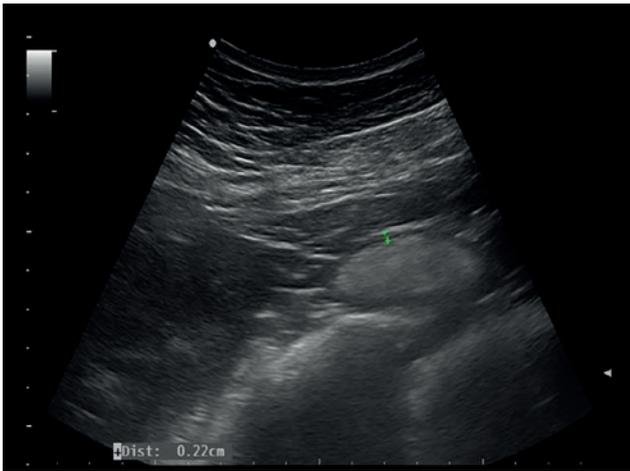


Figure 1. Landmarks used to measure the duodenal wall thickness: from the hyperechoic outer serosal surface to the inner hyperechoic mucosal surface.

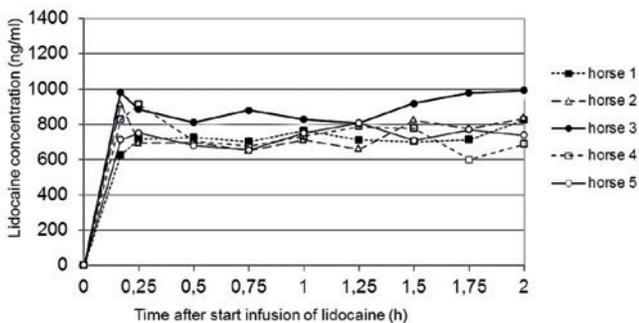


Figure 2. Serum concentrations of lidocaine (ng/ml) during an intravenous infusion of lidocaine (1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes) in five healthy, conscious horses.

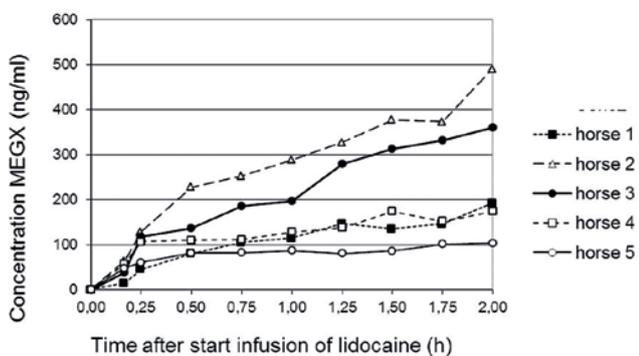


Figure 3. Serum concentrations of MEGX (ng/ml) during an intravenous infusion of lidocaine (1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes) in five healthy, conscious horses.

frozen within one hour after collection (Dasgupta et al., 1996) and was kept at -20°C until analyzed.

The concentrations of lidocaine and MEGX were determined by a validated high-performance liquid chromatography combined with electrospray ionization tandem mass spectrometry as described by Maes et al. (2007).

Statistical analysis

Variables are given as the mean \pm standard deviation (SD). A chi-square test was used to evaluate the effect of treatment on behavior (presence or absence of muscle fasciculation and loss of balance).

A mixed linear model was applied to the other parameters after a Boxcox transformation for the data that did not follow a Gauss distribution. The mixed model included the fixed effects of treatment and time within treatment and the random effect of horse. With this model, a sample size of five horses should be enough to detect significant differences between treatment, with a power of 80% and an alpha error of 5%.

Pearson correlations were computed between all parameters (with the exception of behavior) and the concentrations of lidocaine and MEGX obtained during the lidocaine infusion. The significance level was set at $p < 0.05$. All computations were done on SAS 9.1 (SAS/STAT 9.1 User's Guide. Cary, NC: SAS Institute Inc. 2004).

RESULTS

Serum concentrations of lidocaine and MEGX

No lidocaine nor MEGX were detected in the serum samples collected during the infusion of the placebo.

The concentrations of lidocaine and MEGX obtained from blood samples collected during the infusion of lidocaine are displayed in Figures 2, 3 and 4A.

In all horses, after a rapid increase during the infusion of the bolus, the concentrations of lidocaine reached a steady state. In all horses, the lidocaine concentrations during the steady state ranged between 601ng/ml and 992 ng/ml. The mean lidocaine concentration during the lidocaine infusion was $768.88 \pm 93.32\text{ng/ml}$.

The evolution of the MEGX concentrations presented a larger inter-horse variability with almost a steady state reached after T30 in one horse (horse 5), a continuous but slow increase in two horses (horses 1 and 4) and a quick and continuous increase in two horses (horses 2 and 3). The mean MEGX concentration during the lidocaine infusion was $163.08 \pm 108.98\text{ng/ml}$.

Effects of the infusion of lidocaine and their correlations with the lidocaine/ MEGX concentrations

Behavioral effects

There was a significant effect of treatment (placebo or lidocaine infusion) on the presence of muscle fasciculations ($p \leq 0.001$). None of the horses presented muscle fasciculations during the infusion of the placebo, while four of the five horses presented muscle fasciculations during the administration of lidocaine. In all of those four horses, the muscle fasciculations were noted at T10 and T15, corresponding to the loading dose injection (bolus) and the beginning of the CRI. However, some of the horses also presented muscle fasciculations at other T times. None of the horses showed loss of balance during both infusions.

Respiratory effects

The mean respiratory rate was significantly lower ($p \leq 0.01$) during the lidocaine infusion (8.2 ± 2.5 bpm) than during the placebo infusion (9.0 ± 2.7 bpm), and the decrease in respiratory rate was significantly correlated with the serum MEGX concentration but not with the lidocaine concentration (Table 1 and Figures 4A and 4B).

Cardiovascular effects

There was no effect of treatment on the heart rate (40 ± 8 bpm during the placebo infusion and 38 ± 5 bpm during the lidocaine infusion). There was no correlation between the heart rate and the lidocaine/MEGX concentrations (Figures 4A and B).

The complete examination of the ECG trace before and during the administration of both the placebo and the lidocaine revealed the absence of cardiac arrhythmias.

Despite the absence of influence of treatment on the heart rate, the mean systolic blood pressure was significantly lower ($p \leq 0.001$) during the lidocaine infusion (128.2 ± 17.5 mmHg) than during the placebo infusion (144.3 ± 23.4 mmHg). Similarly, the mean diastolic blood pressure was significantly lower

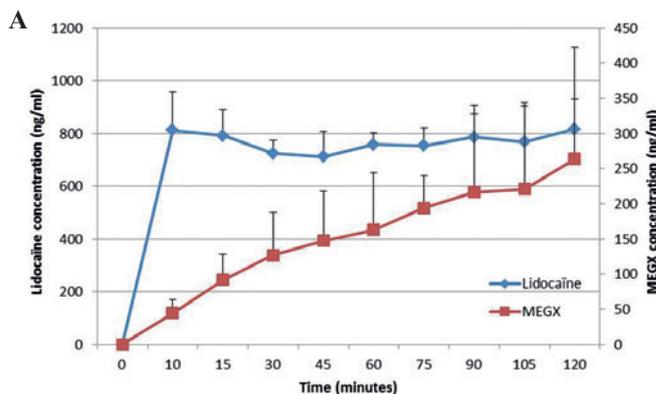


Figure 4A. Evolution of the mean (+ SD) serum concentrations of lidocaine (ng/ml) and MEGX (ng/ml) as a function of time during an experimental intravenous infusion of lidocaine (1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes) in five healthy, conscious horses.

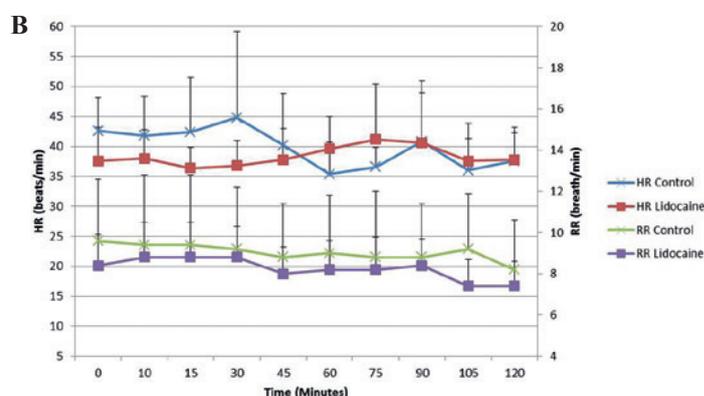


Figure 4B. Evolution of the mean (+ SD) heart rate (HR) and respiratory rate (RR) as a function of time in five horses receiving either a lidocaine infusion at 1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes (lidocaine) or a saline infusion at the same rate (control) during 120 minutes. Bpm = beats/minute.

($p \leq 0.05$) during the lidocaine infusion (89.6 ± 15.9 mmHg) than during the placebo infusion (96.4 ± 18.5 mmHg).

Table 1. Pearson correlation coefficients (r) of the analysis between the tested parameters and the concentrations of lidocaine and MEGX.

Tested parameter		Lidocaine concentration	MEGX concentration
Respiratory rate	r	-0.1838	-0.2586 (*)
Heart rate	r	-0.1123	-0.1415
Systolic blood pressure	r	-0.3578 (**)	-0.3750 (**)
Diastolic blood pressure	r	-0.2537 (*)	-0.2419 (*)
Frequency of the gastrointestinal sounds	r	0.2281 (*)	-0.0094
Frequency of the duodenal contractions	r	0.2574 (*)	-0.0461
Duodenal wall thickness	r	-0.0145	-0.0444

* : $p < 0.05$; ** : $p < 0.001$

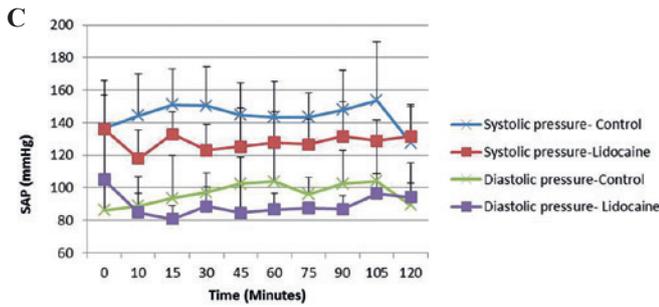


Figure 4C. Evolution of the mean (+ SD) systolic and diastolic systemic arterial pressure (SAP) as a function of time in five horses receiving either a lidocaine infusion at 1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes (lidocaine) or a saline infusion at the same rate (control) during 120 minutes.

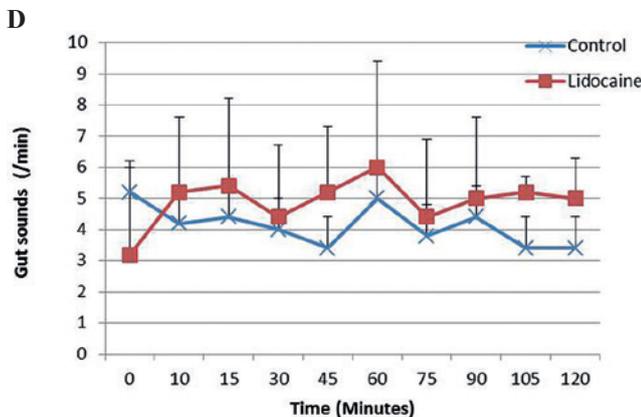


Figure 4D. Evolution of the mean (+ SD) frequency of gut sounds heard in the left flank as a function of time in five horses receiving either a lidocaine infusion at 1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes (lidocaine) or a saline infusion at the same rate (control) during 120 minutes.

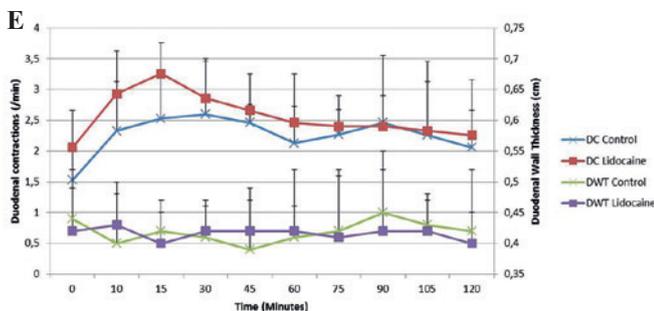


Figure 4E. Evolution of the mean (+ SD) duodenal contraction (DC) and duodenal wall thickness (DWT) as a function of time in five horses receiving either a lidocaine infusion at 1.3mg/kg over ten minutes followed by a continuous rate infusion of 0.05 mg/kg/min during 110 minutes (lidocaine) or a saline infusion at the same rate (control) during 120 minutes.

Both systolic and diastolic arterial blood pressures significantly correlated with both lidocaine and MEGX serum concentrations (Table 1 and Figures 4A and 4C).

Gastrointestinal effects

The mean frequency of the gut sounds heard in the left flank was not significantly different during the treatment with lidocaine (4.9 ± 2.5 borborygmi heard/min) and during the administration of the placebo (4.1 ± 2.2 borborygmi heard/min). However, there was a significant correlation between this clinical parameter and the serum concentration of lidocaine but not of MEGX (Table 1 and Figures 4A and 4D).

The duodenum contractions frequency evaluated by ultrasonography was significantly increased ($p \leq 0.01$) by the treatment with lidocaine (2.6 ± 0.7 contractions/min) compared with the placebo (2.3 ± 0.7 contractions/min). Moreover, this parameter significantly correlated with the serum lidocaine concentration, but not with the MEGX concentration (Table 1 and Figures 4A and 4E). The lidocaine treatment did not significantly influence the duodenal wall thickness. During the placebo infusion, the mean duodenal wall thickness was 0.41 ± 0.05 cm and it was 0.41 ± 0.04 cm during the lidocaine infusion. For this parameter, there were no correlations with the serum lidocaine and MEGX concentrations (Table 1 and Figures 4A and 4E).

DISCUSSION

While the effects of lidocaine have already been extensively evaluated in horses, the present study has the particular purpose of studying the relationship between respiratory, digestive and cardiovascular effects and the serum concentration of lidocaine and its principal metabolite, MEGX. Among the benefits of the present study, the use of conscious, fasted horses was chosen to mimic the clinical conditions of the early postoperative period of colic horses, as clearance of lidocaine has been shown to decrease when horses are fasted (Engelking et al., 1987). The study involved healthy horses in order to evaluate the specific effects of lidocaine/MEGX without a possible modification of the metabolism of lidocaine (and therefore its concentrations) by a pathological process or without the possible interference with other treatments. Ultrasonography, the recording of the ECG via a Holter system and the measurement of the blood pressure by an oscillometric system to evaluate the effects of treatment, were chosen because these methods proved to be reliable in a clinical setting, and because they are non-invasive, which allows reducing the experiment-induced stress and respect animal welfare. Moreover, the study design (saline infusion followed by lido-

caine infusion within the same day rather than given separately), was chosen to respect animal welfare.

Nevertheless, the present study also has several limitations. The study was not totally blinded and the placebo was first administered in all cases in order to avoid meddling of the effects of the residual serum lidocaine concentrations with those of the placebo during the placebo-administration period. However, the principal investigator was not aware of which treatment (lidocaine versus placebo) was administered during the experimental procedure or reading of the recorded parameters. The number of horses in this study was small ($n=5$) but this sample size was confirmed to be sufficient by a power calculation. Another important limitation was the fact that the infusions were performed in a limited period of time (two hours), which can be considered short as in clinical use, the duration of lidocaine infusion is often longer and some effects of lidocaine or its metabolites might have appeared later. Indeed, contrarily to the lidocaine concentrations that reached a steady state after the bolus administration, the concentration of MEGX continued to increase in some horses in the study, and not all of them appeared to reach a steady state after two hours of treatment. However, Dickey et al. (2008) revealed that the MEGX concentrations reached a steady state of approximately 450 ng/ml (higher than all, except one, of the MEGX values in the present study) after 3-6 hours of CRI and did not accumulate over time, while GX, another potentially toxic active lidocaine metabolite, accumulates significantly up to 48 hours. Therefore, the lack of dosage of GX in the present study is also a limitation.

Based on the study by Malone et al. (1998), the administration of 1.3mg/kg of lidocaine as a bolus followed by a CRI of 0.05mg/kg/min permits to reach the therapeutic level of 980 ng/ml (range 1000-2000ng/ml). However, in the present study, concentrations of lidocaine reached the target therapeutic level of 980 ng/ml in only one horse at the end of the bolus (T10) and at the end of the CRI (T120). During the CRI of lidocaine, the other serum lidocaine concentrations ranged from 600 ng/ml to 977 ng/ml (which can be considered as slightly below to below the target level); the toxic level of lidocaine (1850 - 4530 ng/ml (Meyer et al., 2001)) was never reached. Nevertheless, the serum pharmacokinetics of lidocaine and MEGX in the present study were close to those described by Robertson et al. (2005). In studies where lidocaine was administered to pathological or healthy horses as an infusion at the same rate as in the present study, the therapeutic level was sometimes reached (Brianceau et al., 2002; Dickey et al., 2008), and sometimes not (Robertson et al., 2005; Navas de Solís and McKenzie III, 2007; Cook et al., 2008). Several hypotheses may be made to explain the failure to reach the 980 ng/ml in the majority of cases in the present study. As already mentioned, the experiments of the present study were performed over a relatively short period of time and

included only healthy horses. Pathological cases such as horses suffering from postoperative ileus may suffer from endotoxic shock, associated with a decrease in cardiac output and/ or hepatic dysfunction, conditions that have been shown to lead to a decrease of systemic lidocaine turnover (Engelking et al., 1987; McKindley et al., 2002). Furthermore, pathologic horses are susceptible to receiving concurrent drugs that are known to potentially affect the lidocaine metabolism or clearance, such as erythromycin (Orlando et al., 2003), which can also be used as a gastrointestinal prokinetic drug, fluoroquinolones (Isohanni et al., 2005) and cimetidine (Feely et al., 1982). Finally, the serum concentration of 980 ng/ml of lidocaine may not be necessary to produce a therapeutic or toxic effect as lidocaine is protein bound ($53.06 \pm 10.28\%$ of in vitro protein binding of lidocaine in equine plasma at 2 $\mu\text{g/ml}$) and only the unbound drug is available to produce a pharmacological effect (Milligan et al., 2006). In vitro, flunixin and ceftiofur have resulted in increased unbound lidocaine concentrations (Milligan et al., 2006). Low serum protein concentration at the time of lidocaine infusion can also increase the drug available to produce an effect despite no change in total concentration. Unfortunately, the serum protein concentrations were not evaluated in the present study, but they were assumed to be within the normal range as all studied horses were healthy.

In a study conducted in healthy horses by Meyer et al. (2001), lidocaine intoxication was defined as the development of skeletal muscle tremor. In the present study, muscle fasciculations were observed in four of the five studied horses at the beginning of the lidocaine administration (during the loading dose and the beginning of the CRI); these muscle fasciculations disappeared in all cases before the end of the CRI without slowing the rate of infusion. The appearance of toxic signs, despite the low serum concentrations of lidocaine and MEGX, may possibly be caused by a high unbound lidocaine concentration. The timing of appearance of this mild toxic effect of lidocaine may also be explained by the fact that the severity of neurological symptoms caused by lidocaine are probably more dependent on the speed of exposure of brain cells to local anesthetics rather than on a defined blood concentration (Scott 1986; Haasio et al., 1988; Skarda, 1991).

The cardiovascular system of horses is considerably more resistant than the central nervous system to the toxic effects of intravenous lidocaine (Meyer et al., 2001; Wagman et al., 1967). Therefore, when lidocaine is used at the usual clinical dosage, few cardiovascular side effects have been reported. In the present study, lidocaine infusion did not modify the heart rate of the five healthy, awake horses, as was found in other studies conducted at the same dosage in conscious, healthy (Rusiecki et al., 2008) or colic horses (Malone et al., 2006), in healthy horses overdosed in lidocaine until the onset of the first signs of intoxication.

tion (muscle fasciculations) (Meyer et al., 2001) and in horses anesthetized for castration (Murrell et al., 2005) or for colic surgery (Feary et al., 2006). Administered at the dose of 1.3 mg/kg in bolus followed by a CRI of 0.05 mg/kg/min, lidocaine is not known to produce cardiac arrhythmias, as was the case in the present study. However, Mullen et al. (2009) reported a case of supraventricular tachycardia and auriculoventricular blocks in a horse with colic treated with lidocaine infusion at the usual dosage. The authors of this report suggested that the arrhythmias were caused by the abdominal distention, which is hypothesized to cause vagal stimulation in horses (Abutarbush, 2006) in combination with a mechanism (Lieberman et al., 1968), by which lidocaine increases sinoatrial nodal discharge rate. The low doses of xylazine and butorphanol administered to this horse one hour before starting the lidocaine treatment may also have contributed to the development of the arrhythmias (Mullen et al., 2009). Based on their observations, Mullen et al. (2009) advised that horses that develop skeletal muscle fasciculations during treatment with lidocaine should be evaluated for cardiac arrhythmias. If the arrhythmias appear, lidocaine administration should be slowed or discontinued. However, in a study, in which horses were administered an overdose of intravenous lidocaine until the onset of clinical signs of intoxication (muscle fasciculations), no arrhythmias were observed (Meyer et al., 2001).

In the aforementioned study by Meyer et al. (2001), lidocaine did not significantly modify the mean systolic and diastolic blood pressures. The mean arterial blood pressure was neither modified by the administration of lidocaine in a protocol of experimentally induced endotoxemia in conscious horses (Peiro et al., 2010), nor in horses anesthetized for colic surgery (Feary et al., 2006). On the contrary, lidocaine and MEGX were associated with a significant decrease of the systolic and diastolic blood pressures in the present study. Nonetheless, the blood pressure values obtained here were all within or slightly above the published ranges of normal values taken non-invasively at the coccygeal artery of resting horses (Parry et al., 1984). Therefore, although statistically significant, this hypotensive effect could be considered as clinically irrelevant. To the authors' knowledge, a severe lidocaine-induced hypotension in equids has only been described when a large and rapid lidocaine overdose was systemically delivered, i.e. 5 mg/kg administered intravenously over five minutes to ponies anesthetized with halothane (Doherty and Frazier, 1998). This hypotensive effect may be caused by the vasoactive (vasodilator) properties of the lidocaine (Demaria et al., 2003).

In *in vitro* studies, it has been demonstrated that lidocaine enhances the contractility of intestinal smooth muscle (Nieto et al., 2000; Guschlbauer et al., 2010; Tappenbeck et al., 2013). On the other hand, lidocaine has been shown to decrease the duration of

(postoperative) ileus in clinical studies on horses suffering from colic (Malone et al., 2006; Torfs et al., 2009). However, using the usual lidocaine dosage of the aforementioned studies, other authors failed to demonstrate a prokinetic effect of lidocaine on clinically normal horses by the placement of bipolar electrodes on the proximal jejunum to record the migrating myoelectrical complexes (Milligan et al., 2007) or by the administration of barium-filled microspheres by nasogastric intubation (Rusiecki et al., 2008). Therefore, the beneficial effects of lidocaine on intestinal motility in horses suffering from ileus were supposed to be more attributable to its anti-inflammatory effects than to its prokinetic or analgesic effects (Cook and Blikslager, 2008). Indeed, the visceral analgesia provided by systemically administered lidocaine has been shown to be ineffective in studies on horses (Robertson et al., 2005; Cook et al., 2008). Surprisingly, in the present study, a positive correlation value of the coefficient was found between the concentrations of lidocaine and the frequencies of the borborygmi auscultated in the left flank and of the duodenal contractions evaluated by ultrasonography. Even if the correlation with the borborygmi can be somewhat debatable as the auscultation of the intestinal gut sounds in only one place in the left flank is not very accurate nor sensitive, the result on the duodenal contractions cannot be so controversial. It can be assumed to be related to the initial peak of contractions observed after the administration of the bolus. The evaluation of the duodenum in the present study was chosen for two reasons: First, it is a part of the intestine that suffers frequently from distention when horses suffer from ileus, and thus it is an interesting zone for evaluating the effect of lidocaine. Secondly, the ultrasonography of this region allows a quantifiable and objective evaluation of the intestinal motility as the same part of the intestine, the duodenum, can be almost constantly visualized using the same ultrasonographic window (Kirberger et al., 1995). The results are in contrast with the results of a study by Brianceau et al. (2002), in which no effect of lidocaine on the duodenal contractions frequency was found. However, that study was performed in horses that underwent colic surgery, using a scoring system for the evaluation of the duodenum motility attributing the score 0 every time there was 0 to 3 duodenal contractions per minute rather than taking into account the number of contractions per minute. However, fasted horses have less contractions of the duodenum than fed horses (Kirberger et al., 1995). Therefore, this scoring system may have masked a mild effect. Although the horses of the present study were fasted, the number of duodenal contractions during both the placebo and the lidocaine infusions were closer to the number of duodenal contractions of fed horses than to those of the starved horses in the Kirberger study (1995). In the present study, the horses were subjected to a twelve-hour fasting period, whereas the horses

in the Kirberger study (1995) were fasted during 36 hours. This suggests that twelve hours of fasting is probably too short to reduce the intestinal motility of the duodenum. It would be interesting to verify if the prokinetic effect of lidocaine would still be observed after a longer fasting period.

In conclusion, in this study, it was shown that lidocaine administered intravenously at the usual clinical dosage induces a clinically non-significant systemic arterial hypotension, which is correlated with both serum lidocaine and MEGX concentrations, and stimulates the frequency of duodenal contractions, which is correlated to the serum lidocaine concentration. Further studies using longer infusion durations and/ or longer fasting periods in a larger population of horses are warranted to confirm these results.

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