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General Articles

Effects of intravenous lidocaine overdose on cardiac electrical activity and blood pressure in the horse

G. A. MEYER*, H. C. LIN, R. R. HANSON and T. L. HAYES†

Auburn University College of Veterinary Medicine, Department of Large Animal Surgery and Medicine, McAdory Hall, Auburn, Alabama 36849-5522, USA.

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Summary

This study aimed to identify blood serum lidocaine concentrations in the horse which resulted in clinical signs of intoxication, and to document the effects of toxic levels on the cardiovascular and cardiopulmonary systems. Nineteen clinically normal mature horses of mixed breed, age and sex were observed. Lidocaine administration was initiated in each subject with an i.v. loading dose of 1.5 mg/kg bwt and followed by continuous infusion of 0.3 mg/kg bwt/min until clinical signs of intoxication were observed. Intoxication was defined as the development of skeletal muscle tremors. Prior to administration of lidocaine, blood samples for lidocaine analysis, heart rate, mean arterial blood pressure, systolic blood pressure, diastolic blood pressure, respiratory rate and electrocardiographic (ECG) data were collected. After recording baseline data, repeat data were collected at 5 min intervals until signs of intoxication were observed.

The range of serum lidocaine concentrations at which the clinical signs of intoxication were observed was 1.85–4.53 µg/ml (mean ± s.d. 3.24 ± 0.74 µg/ml).

Statistically significant changes in P wave duration, P-R interval, R-R interval and Q-T interval were observed in comparison to control values, as a result of lidocaine administration. These changes in ECG values did not fall outside published normal values and were not clinically significant. Heart rate, blood pressures and respiratory rates were unchanged from control values. This study establishes toxic serum lidocaine levels in the horse, and demonstrates that there were no clinically significant cardiovascular effects with serum lidocaine concentrations less than those required to produce signs of toxicity.

*Author to whom correspondence should be addressed. Present address: Cliffe Veterinary Group, Radstock House, 21 Cliffe High Street, Lewes, East Sussex BN7 2AH, UK. †Present address: Illinois Equine Hospital, 5045 Eola Road, Naperville, Illinois 60563, USA.

Introduction

Lidocaine was first synthesised in 1943, since when it has been used as a local anaesthetic and cardiac anti-arrhythmic drug (Stenson *et al.* 1971; Tanelian and MacIver 1991; Hondeghem and Mason 1992). In human medicine, it has also been used to treat a variety of conditions, e.g. pain, seizures and postoperative ileus (Lemmen *et al.* 1978; Petersen *et al.* 1986; Petersen and Kastrup 1987; Rey *et al.* 1990; Rimback *et al.* 1990; Aggarwal and Wali 1993; Cogar 1997; Fishman 1997; Groudine *et al.* 1998).

Recently, in equine medicine, there has been growing interest in the application of continuous infusion i.v. therapy in the treatment of postoperative ileus (Malone 1998). Lidocaine i.v. may provide long-term analgesia in selected neurological conditions in the horse. As a result of this new interest, questions have been raised as to the maximum safe systemic dose that can be administered and what effects are produced if this dose is exceeded. Literature review for data on blood lidocaine levels that produce symptoms of intoxication indicates that a wide species variation exists. Data on toxic blood levels for lidocaine in the horse are incomplete and published information appears to be extrapolated from canine data (Skarda 1991).

The intent of this study was to identify blood serum lidocaine concentrations in the horse resulting in clinical signs of toxicity and to document any behavioural, cardiovascular or cardioelectrical anomalies associated with i.v. administration.

Materials and methods

Horses

Nineteen mature horses (10 mares, 9 geldings) of mixed breed age (3–18 years) and mean weight 410 kg were studied. These individuals were free of disease and had current tetanus, equine herpesvirus-1 and -4, Eastern equine encephalitis (EEE), Western equine encephalitis (WEE) and equine influenza vaccination status. This study was reviewed and approved by the Institute Animal Care and Use Committee of Auburn University.

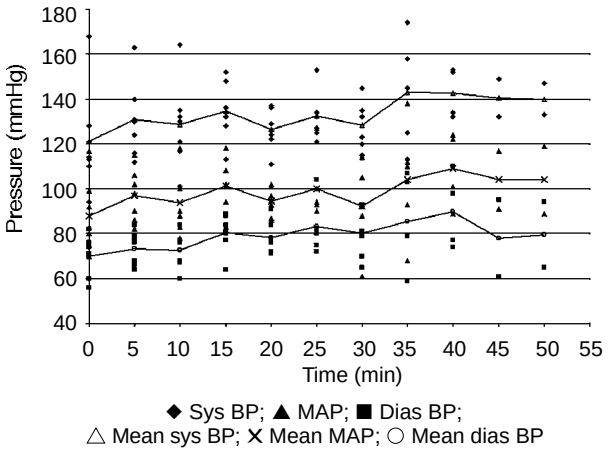

*Fig 1: Systemic arterial blood pressures during the course of i.v. lidocaine administration (*Trial 2*). Sys BP= systolic blood pressure; dias BP= Diastolic blood pressure; MAP = mean arterial pressure.*

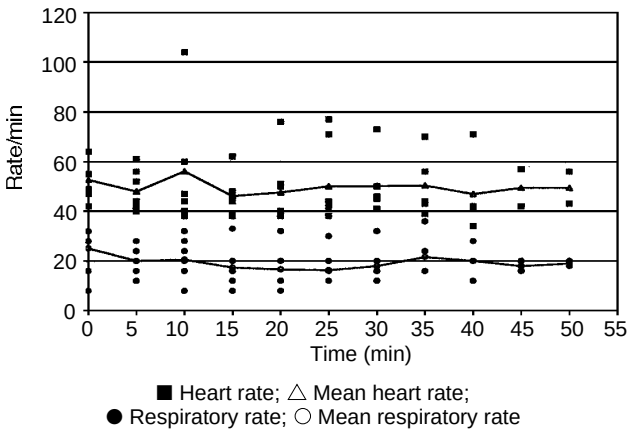

*Fig 2: Heart and respiratory rates during the course of i.v. lidocaine administration (*Trial 2*).*

Experimental design

Each horse in the study had one 14 gauge Teflon indwelling catheter (Abocath)[1] placed aseptically in each jugular vein, the left used for lidocaine administration and the right for blood sample collection. Prior to the administration of lidocaine HCL 2% solution[1], blood samples for lidocaine analysis, arterial blood pressures, respiratory rate and ECG data were collected for utilisation as control values. After collection of baseline data, i.v. administration was started and repeat blood samples for further analysis and measurements of data collected at 5 min intervals until clinical signs of toxicity were observed, defined as the development of skeletal muscle fasciculation. Two separate trials involving all 19 horses were performed, using 2 different lidocaine administration regimens in each trial. Both administration regimens were calculated to produce a steady state blood lidocaine concentration of 5.73 µg/ml. A period of 14 days separated the 2 trials to ensure that there were no residual effects of the previous trial.

Trial 1: Lidocaine administration was initiated in each of the 19 subjects with a loading dose of 2% lidocaine i.v. 1.5 mg/kg bwt administered over a 3 min period, followed by continuous i.v. infusion of 2 mg/ml lidocaine solution, a rate calculated to provide 0.3 mg lidocaine/kg bwt/min and administered until clinical signs of toxicity were observed.

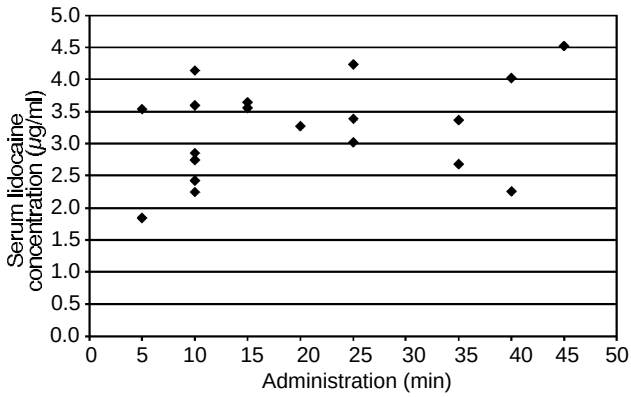

*Fig 3: Serum lidocaine concentrations that resulted in development of clinical signs of toxicity (*Trial 2*).*

Trial 2: Lidocaine administration was initiated in each of the 19 subjects with continuous i.v. infusion of 2 mg/ml lidocaine solution, 0.3 mg lidocaine/kg bwt/min and administered until clinical signs of toxicity were observed.

The 2 mg/ml lidocaine solution was compounded by adding 110 ml injectable 2% lidocaine hydrochloride solution to 1 litre balanced electrolyte solution[1]. This was administered by a calibrated i.v. fluid pump (LifeCare Model 4 Pump)[1].

Blood pressure: Blood pressure data were collected using a noninvasive oscillometric system (Dynamap)[2]. The inflatable cuff for the blood pressure measurement equipment was positioned at the base of the tail and centred over the coccygeal artery.

Blood analysis: Blood samples were collected for lidocaine analysis in sterile glass blood collection tubes (Vacutainer)[3] containing no anticoagulant. Within 6 h of collection, serum was separated by centrifugation, transferred into polypropylene vials (CryoTube: Nalgene)[5] and frozen at -80°C until analysed. Lidocaine analysis was performed via high performance liquid chromatography (HPLC) (Nattel *et al.* 1979; Nution *et al.* 1979).

ECG analysis: Data were collected in base-apex configuration and recorded on a paper strip chart at a rate of 50 mm/s. The recorded strip charts were measured manually and data digitised. P wave duration, P-R interval, QRS duration and Q-T interval data were analysed.

Statistical analysis

One way ANOVA was utilised to evaluate all ECG and cardiopulmonary data.

Results

Electrocardiogram (ECG)

In both *Trials 1* and *2*, ANOVA analysis of P wave duration ($P = 0.02$), P-R interval ($P<0.001$), Q-T interval ($P<0.001$) showed statistically significant variation throughout the course

of the study, but these values did not fall outside published normal ranges (Patterson 1996). QRS duration (P = 0.61) remained unchanged during the course of each study.

Cardiopulmonary

In both *Trials 1* and *2*, ANOVA analysis of mean arterial pressure (P= 0.5), systolic pressure (P= 0.42), diastolic pressure (P = 0.06), heart rate (P = 0.97) and respiratory rates (P = 0.59) were unchanged during the course of the study (Figs 1 and 2).

Lidocaine concentration

Serum lidocaine concentrations in *Trial 2*, at the point at which muscle fasciculations were observed, ranged between 1.85–4.53 µg/ml (mean ± s.d. 3.24 ± 0.74 µg/ml; Fig 3). ANOVA analysis of toxic lidocaine levels obtained from *Trial 1* compared to *Trial 2* showed no statistical difference between the 2 (P = 0.67); mean ± s.d. period for development of clinical signs of toxicity was 11.36 ± 5.52 min in *Trial 1* and 33.12 ± 8.84 min in *Trial 2*.

Behaviour

In both trials, some alteration in behaviour was observed at the terminal stages of our tests. Two individuals displayed behaviour interpreted as alteration in visual function, of rapid but intermittent eye blinking, anxiety and attempts to inspect closely located objects. One individual developed rapid onset of severe ataxia and collapsed into sternal recumbency moments after the onset of eye blinking. This individual recovered within 10 min of stopping lidocaine administration and was able to rise and walk unassisted. Seven individuals appeared mildly sedated at the approximate midpoint of the test. The remaining individuals displayed no overt changes in behaviour.

Discussion

Serum lidocaine concentrations resulting in clinical signs of toxicity in our study were substantially lower than the 8 µg/ml level published previously (Skarda 1991). Toxicity studies in man and dogs produced muscle fasciculations at mean ± s.d. serum lidocaine concentrations of 1.56 ± 0.61 µg/ml and 8.21 ± 1.69 µg/ml, respectively (Wilcke *et al.* 1983; Wallace 1997) The findings of our study, in comparison to human and canine data, demonstrate the significant differences between species with regard to toxic lidocaine concentrations. Two separate trials were performed in this study with different lidocaine administration rates, because of concerns that the administration regimen applied in *Trial 1* may have been too rapid. This proved to be unfounded. Overly rapid lidocaine administration rates can result in CNS stimulation related to exposure of the brain to lidocaine rather than a defined blood concentration (Scott 1986; Haasio *et al.* 1988). Although observed more quickly in *Trial 1* than *Trial 2*, ANOVA analysis of blood lidocaine concentrations at which development of muscle fasciculations occurred were no different.

In man, lidocaine has been shown to cause a dose-dependent arterial vasoconstriction at serum concentrations 10–102 ng/ml (Klein *et al.* 1968). In addition, it has been demonstrated in dogs that serum lidocaine concentrations approaching levels that produce CNS signs result in an increase in heart rate and a decrease in arterial blood pressure (Liu *et al.* 1980). The nonsignificant increases in blood pressure and heart rate observed in our study indicate that the equine cardiovascular system is not as sensitive to the effects of systemically administered lidocaine as other species. Our data also show that the nervous and/or musculoskeletal system of the horse is more sensitive to the effects of systemically administered lidocaine than is the cardiovascular system.

It is unknown why one individual in this study developed rapid and profound ataxia that progressed to collapse. This individual was the oldest member in the study, age 15–18 years as determined by dental examination. It is well documented that lidocaine is metabolised in the liver and, in neonates, the elderly, or debilitated individuals, liver function can be impaired, resulting in elevated blood lidocaine levels developing over time. Because of the short duration of drug administration to this individual (10 min), it is unlikely that impaired hepatic clearance would have any effect in this situation. Serum lidocaine concentration in this subject at the time of collapse was 2.86 µg/ml, which was approximately median in values recorded. After the collapse of this individual, lidocaine administration was discontinued and the subject's condition monitored. The subject maintained consciousness with no expression of seizure activity. Cardiovascular and cardiopulmonary anomalies were also not detected during the recovery period and, within 10 min of the discontinuation of lidocaine administration, the individual was able to rise and walk unassisted. This rapid recovery from the effects of lidocaine overdose is consistent with the author's observations of overdose in clinical patients when administration errors have been made, and is compatible with the short 40 min half-life of lidocaine in the horse (Engelking *et al.* 1987). Lidocaine administration i.v. in man has been shown to result in changes in mentation, lightheadedness and visual and auditory disturbances (Hazra 1971; Liu *et al.* 1980; den Hartigh *et al.* 1993; Ueda *et al.* 1993; Haginomori *et al.* 1995; Shiomi *et al.* 1997a,b; Wallace 1997). The alterations in behaviour observed subjectively in several of our horses in the final stages of this study were consistent with these previously reported effects in man. This study establishes toxic serum lidocaine levels for the horse, and demonstrates that there are no clinically significant cardiovascular effects with serum lidocaine concentrations lower than those that result in signs of toxicity. The target steady state serum lidocaine level commonly used in clinical treatment of ileus in the horse is 0.98 µg/ml (Malone 1998; Meyer and Hanson 2000). This study indicates that the toxic threshold in the horse is 2–3 times the target therapeutic level used in the treatment of ileus in the horse.

Manufacturers' addresses

[1]Abbott Laboratories, North Chicago, Illinois, USA.
[2]Critikon, Inc; Tampa, Florida, USA.
[3]Becton Dickinson, Franklin Lakes, New Jersey, USA.
[4]Cole-Parmer, Vernon Hills, Illinois, USA.

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