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Observation of potential lidocaine toxicity during local anesthesia administration for punch skin biopsy in dogs

Nikša Lemo[1]*, Dražen Vnuk[2], and Frane Banović[3]

[1]*Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia*

[2]*Clinic for Surgery, Orthopaedics and Ophthalmology, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia*

[3]*Department of Small Animal Medicine and Surgery, Veterinary Medical Center, University of Georgia, College of Veterinary Medicine, Athens, GA, USA*

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ABSTRACT

Punch biopsies are a widely used diagnostic method in veterinary dermatology. During a biopsy, it is necessary to use local anesthesia and/or sedation to prevent pain. Lidocaine is a local analgesic drug that is often used. Adding adrenaline to lidocaine solutions for local anesthesia potentiates and prolongs its analgesic action. Intravenous lidocaine administration has been reported to cause significant side effects, seizures being considered the most common sign of intoxication, while bradyarrhythmia and conduction disturbances are less prevalent. The aim of this study is to investigate the potential lidocaine toxicity effect of two frequently used local anesthetic solutions, lidocaine and lidocaine/adrenaline combination. Nine healthy dogs were randomly assigned into two groups. One group (n = 4) received subcutaneous injections of lidocaine (total of six 1 mL injections of 2 % lidocaine solution), while the dogs in the second group (n = 5) received a lidocaine/adrenaline combination (total of six 1 mL injections of 2 % lidocaine solution plus 0.0125 mg adrenaline tartarate). None of the known lidocaine side effects were observed. The blood concentration of lidocaine was far below the reported convulsive threshold in dogs. Subcutaneous administration of two different lidocaine local anesthetic formulations was shown to be well tolerated and safe. This research suggests that lidocaine and lidocaine/adrenaline formulation can be safely used as a local anesthetic for skin punch biopsies in dogs with body mass greater than 5 kg.

Key words: lidocaine, adrenaline, toxicity, punch biopsy, serum concentration

*Corresponding author:

Nikša Lemo Assoc. Prof, dipl ECVD, DVM, MSc, PhD. Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb, Heinzelova 55, 10000 Zagreb, Croatia, +385 1 2390 341; Fax: +385 1 2390 341; E-mail: nlemo@vef.hr

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Introduction

Skin biopsy techniques have been widely used as a diagnostic method in veterinary dermatology, particularly when dealing with an unfamiliar clinical presentation or a case that progresses or relapses despite seemingly appropriate empirical therapy (YAGER and WILCOCK, 1988). The simplest and quickest method of skin biopsy involves the use of a punch biopsy technique (HENFREY et al., 1991; CURTIS, 2001), during which it is necessary to use subcutaneous injections of local anesthetics and/or sedation to control pain in dogs (SKARDA, 1998).

Lidocaine is a local anesthetic, which, due to its rapid onset of action, low cost and wide availability, is commonly used, in veterinary dermatology. It is applied in a variety of ways; topically (by local subcutaneous infiltration, epidural injection, nerve block) or by intravenous injection into a peripheral vein to provide limb analgesia (DUKE, 2000). Lidocaine also has an anti-arrhythmic effect, being sometimes used for the acute control of life-threatening ventricular arrhythmia in dogs and cats (LUNNEY and ETTINGER, 1995). Furthermore, intravenous lidocaine administration has been reported to cause significant side effects (WILCKE et al., 1983; LUNNEY and ETTINGER, 1995); seizures being considered the most common sign of intoxication, while bradyarrhythmia and conduction disturbances are less prevalent (WILCKE et al., 1983; LUNNEY and ETTINGER, 1995). Adrenaline is commonly co-administered with lidocaine in some local anesthetic formulations. Adding adrenaline to lidocaine diminishes local blood flow and therefore lidocaine clearance (SCOTT et al., 1972; SINNOTT et al., 2003), prolonging lidocaine's action in a dose-related manner (LIU et al., 1995). In addition, the higher pH of the lidocaine-adrenaline solution could reduce pain on injection in humans (COLARIC et al., 1998).

Recently, seizures occurred in two dogs with body mass of less than 5 kilograms (kg) in association with the administration of subcutaneous lidocaine and intravenous sedative medetomidine for the purpose of acquiring several skin punch biopsies (RAINGER et al., 2009). The authors recommended not to exceed the toxic lidocaine dose of 11 mg/kg in dogs for local anesthesia due to possible side effects (RAINGER et al., 2009). To the author's knowledge, there are no studies describing the potential systemic toxicity of subcutaneous lidocaine injections provided for skin biopsies in dogs.

The primary objective of this noninvasive study was to investigate the potential lidocaine toxicity effect of two frequently used local anesthetic solutions, lidocaine and lidocaine/adrenaline, provided for punch skin biopsy procedure in dogs with body mass higher than 5 kg. The second aim of this study was to compare the clinical toxic effects and systemic lidocaine absorption after administration of these two local anesthetics.

Materials and methods

The study protocol was approved by the Research Committee of the Faculty of Veterinary Medicine, University of Zagreb, and followed the national legislation on the care and use of laboratory animals. Written informed consent was obtained from each owner. The methodology in this study followed the skin biopsy punch technique recommended for veterinary practitioners (HENFREY et al., 1991; CURTIS, 2001).

Nine healthy dogs (6 males and 3 females) older than 3 months, with a minimum mass of 5 kilograms that presented to the Clinic for Internal Medicine, Faculty of Veterinary Medicine, University of Zagreb, were randomly assigned via a computer-generated list, into two groups. One group received subcutaneous injections of lidocaine (group L; n = 4), while the dogs in the second group were given a lidocaine/adrenaline combination (group L+A; n = 5). Clinical examination and basic laboratory work (hematology and biochemistry panel), performed on all dogs before entering the study, revealed no abnormalities. No oral and/or topical medications were permitted to be given to any dog 4 weeks prior to inclusion in the study.

Following the recommendation to collect a minimum of 5 punch biopsies from each dog to ensure that the samples actually represent the pathogenic process in question (LINDER, 2001), three symmetrical cutaneous body sites per each dog (total of 6 skin punch sites) were selected for the skin punch biopsy procedure, using a disposable sterile 8-mm biopsy punch. The sites were gentle clipped and outlined with a marker pen before administration of the local anesthesia. Each selected symmetrical body site (scapula region, the lower level of last rib, and loins) was undermined with 1 milliliter (mL) of the appropriate local anesthetic, according to the study randomization, injected subcutaneously through a 2 mL syringe with a 25-gauge needle. Each dog in group L received a total of six 1 mL injections of 2 % lidocaine solution (Lidokain 2 %, Belupo, HR; 1 mL contains 20 milligrams (mg) of lidocaine), while each animal in group L+A was given a different anesthetic solution that contained additional adrenaline (Lidokain-adrenalin, Belupo, HR; 1mL contains 20 mg lidocaine and 0.0125 mg adrenaline tartarate). After a local anesthesia injection, it is recommended to allow enough time, usually 5 minutes, for the lidocaine to reach full effect before beginning the procedure with the biopsy punch. The act of performing the full-thickness skin punch and acquiring the skin biopsy specimen was not deemed necessary for the objectives of this study.

As soon as the dogs were locally anaesthetized, the time of the procedure was noted as time 0. Any potential adverse toxic clinical effects due to the administration of anesthetic lidocaine (WILCKE et al., 1983; LUNNEY and ETTINGER, 1995; RAINGER et al., 2009) (i.e. tremors, convulsion, and myoclonic movements) were recorded during the entire observation time, from 0 to 120 minutes. An intravenous catheter (20, 22 or 24 G depending on the size of the dog) was inserted into the cephalic vein, and a 3.5

milliliter (mL) blood sample was collected, in accordance with the following schedule: before application of local anesthetic injections (0 minutes) and after 10 minutes, 30 minutes, 60 minutes, 90 minutes and 120 minutes. The blood samples were centrifuged (3000/min) to collect the serum. Serum lidocaine concentrations were measured by gas chromatography-mass spectrometry as previously described (LEMO et al., 2007)

For statistical evaluation, STATISTICA 7.0 (StatSoft Inc., Tulsa, OK, USA) was used. The differences in the type of treatment (lidocaine or lidocaine+adrenaline) at the same time points were assessed by the Mann-Whitney U test and the differences between each pair of groups at different time points by the Newman-Keuls test. The influence of predictor variables, such as gender, mass, age and type of treatment, on the lidocaine serum concentration time was assessed by the general regression model, and the results were expressed as Pareto charts of *t*-values. A P-value of <0.05 was considered significant.

Results

The signalment and lidocaine dosage data for the 9 dogs included in the study are summarized in Table 1.

Table 1. Signalment features and lidocaine dosage in 9 dogs included in the study

Dogs	Treatment group	Breed	Age (months)	Sex	Mass (kg)	Lidocaine dosage (mg/kg)
Dog 1	Group L	Mixed breed	60	F	13.5	8.8
Dog 2	Group L	Mixed breed	54	F	19.0	6.3
Dog 3	Group L	Alaskan malamute	72	M	52.0	2.3
Dog 4	Group L	Golden Retriever	84	M	48.0	2.5
Dog 5	Group L+A	Poodle	168	M	10.7	11.2
Dog 6	Group L+A	Mixed breed	36	M	18.0	6.6
Dog 7	Group L+A	Mixed breed	36	F	8.0	15.0
Dog 8	Group L+A	Boxer	120	M	26.5	4.5
Dog 9	Group L+A	Mixed breed	12	M	32.0	3.75

L, lidocaine; L+A, lidocaine plus adrenaline; M, male; F, female; mg, milligram; kg, kilogram

No significant differences in body mass existed between the two groups (33.1 ± 19.6 kg for the lidocaine-treated dogs vs. 20.8 ± 10.1 kg for the lidocaine plus adrenaline treated dogs; P = 0.26). The mean lidocaine dose given to dogs in Group L was 4.9 mg/kg (range 2.5 - 8.8 mg/kg) while the mean lidocaine dose for Group L+A was 8.2 mg/kg (range 3.75 - 15 mg/kg). None of the known lidocaine side effects, such as tremors, convulsions or myoclonic movements, or any other abnormalities were observed in any dog during the follow up of 120 minutes after the subcutaneous anesthetic administrations. The highest mean value of serum lidocaine concentration in Group L was observed 30 minutes after administration (0.48 μg/mL) while the lowest concentration was measured

after 10 minutes (0.27 µg/mL) (Fig. 1). At 120 minutes, the mean serum lidocaine level in Group L was 0.35 µg/mL. In the presence of adrenaline (Group L+A), serum lidocaine concentrations increased linearly, reaching a peak concentration after 60 minutes of exposure (mean value of 0.72 µg/mL) and then decreased slightly over the following 60 minutes, reaching a mean value of 0.53 µg/mL at 120 minutes after administration (Fig. 1).

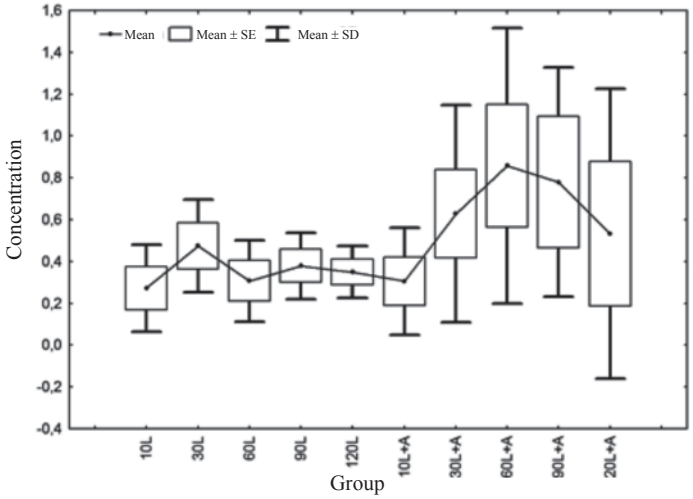

Fig. 1. Box and whisker plot of the lidocaine serum concentrations in micrograms/microliter (µg/mL) in the dogs treated with lidocaine in the absence (L) or presence (L+A) of adrenaline for exposure periods from 10 to 120 minutes

With the exception of the 10-minute exposure period, lidocaine serum levels were higher in the presence of adrenaline (Group L+A) for all exposure times; the highest difference in the mean values was observed at 60 minutes after the anesthetic administrations. No statistical significance was observed using the Man-Whitney U test between the two types of the treatments, comparing exposure periods at 10 minutes ($P = 0.66$), 30 minutes ($P = 0.83$), 60 minutes ($P = 0.52$), 90 minutes ($P = 0.88$) and 120 minutes ($P = 0.56$). Furthermore, there was no significant difference observed between different time periods for any tested pairs of the groups according to the Newman-Keuls test. The Pareto charts of t values of the predictor variables for each exposure period are presented in Fig. 2. Selected predictor variables (age, gender, mass and type of treatment) had the lowest influence at 10 and 120 minutes of exposure to lidocaine in the presence/absence of adrenaline (Fig. 2). However, the results of the general regression model showed that none of the predicted variables had any statistically significant influence on lidocaine serum concentration.

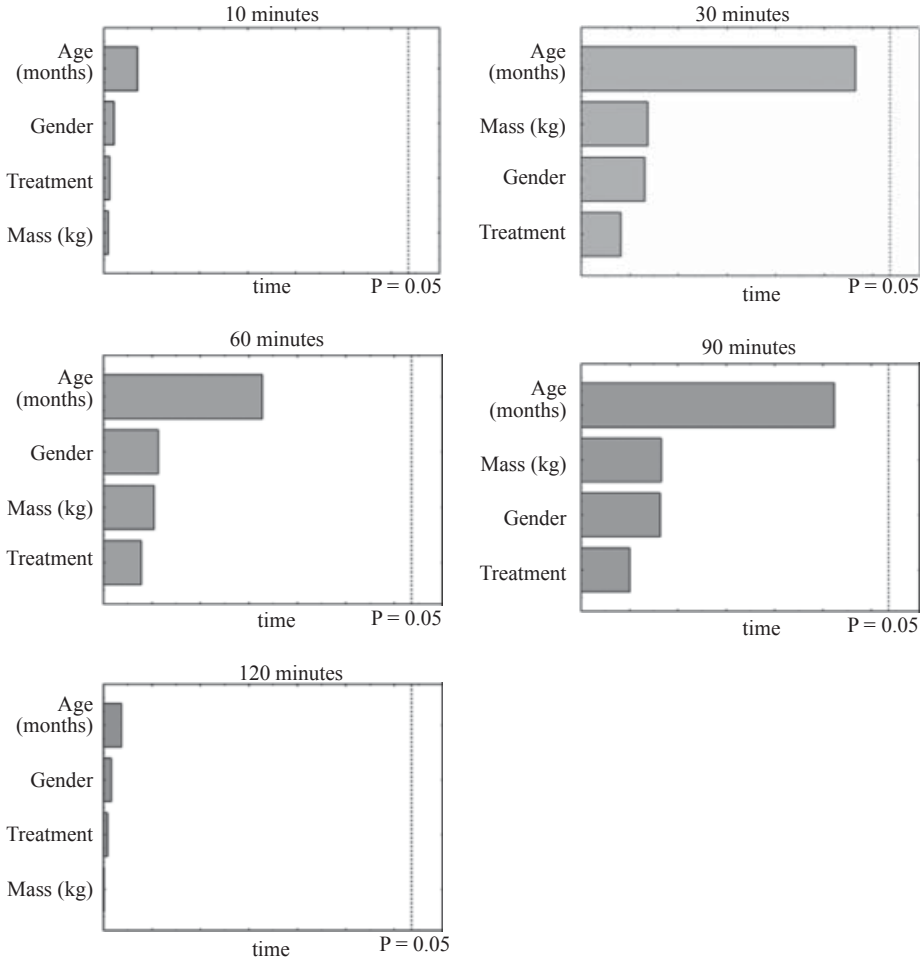

Fig. 2. Pareto charts of t values of the predictor variables (age, gender, mass, treatment) for each exposure period (10, 30, 60, 90, 120 minutes)

Discussion

Lidocaine is one of the most widely used local anesthetic agents in veterinary practice, with a mechanism of action targeting the cell membrane, thereby preventing the generation and the conduction of nerve impulses. Despite the apparent safety of lidocaine, there are a few reports of local anesthetic toxicity in infants and children (DONALD and DERBYSHIRE,

2004; MORAN et al., 2004; ALFANO et al., 1984). The most common toxic reaction from lidocaine is excitation of the central nervous system (i.e. drowsiness, dizziness, agitation, seizures) (SKARDA, 1998). Toxic reactions from subcutaneous injections occur later, because the peak time for subcutaneous absorption is 15 to 30 minutes, depending on the anatomic location and the use of adrenaline (SCOTT et al., 1972). In human medical literature, it was suggested that the subcutaneous lidocaine dosage should be limited to 4.5 mg/kg or 7 mg/kg when used with or without the vasoconstrictor adrenaline (ALFANO et al., 1984; RYAN et al., 1993). Importantly, these lidocaine dosage recommendations were not substantiated by any detailed studies correlating lidocaine serum concentrations after subcutaneous injections and toxic effects.

In this report, we determined the serum lidocaine concentrations, with no lidocaine associated toxic effects, from two different lidocaine formulations, for the purpose of subcutaneous local anesthesia in canine skin biopsies. In our study, none of the dogs experienced any known lidocaine side effects, such as tremors, convulsions or myoclonic movements. Furthermore, the blood concentration of lidocaine in our study was far below the reported convulsive threshold in dogs (47 µg/mL) after intravenous lidocaine administration (FELDMAN et al., 1989); the highest serum concentration of lidocaine was 0.76 µg/mL for Group L (dog 1 at 30 minutes) and 1.73 µg/mL for Group L+A (dog 9 at 60 minutes), respectively. However, seizures in people have been associated with plasma lidocaine levels between 5 and 15 µg/mL (ALFANO et al., 1984; AHMED et al., 2004) and in one dog with a lidocaine level of 2.3 µg/mL (RAINGER et al., 2009). These particularly sensitive individuals likely have an abnormal metabolism and high plasma levels of the lidocaine metabolites monoethylglycinexilidide and 2.6-glycine xylide, which may be responsible for seizure side effects (DE TOLEDO, 2000).

Lidocaine levels can be affected by several factors, such as drug interactions, hepatic metabolism and even the site of injections, due to possible increased vascularity in certain body areas. Furthermore, lidocaine levels can be influenced by using adrenaline in combination with lidocaine, where local vasoconstriction from the adrenaline delays the absorption of lidocaine. The maximum serum lidocaine levels in Group L were achieved after 30 minutes, which is in accordance within human studies, while in Group L+A the peak was delayed for another 30 minutes (maximum level at 60 minutes) confirming the effect of adrenaline on lidocaine systemic absorption (SCOTT et al., 1972).

There are only rare reports of lidocaine-associated toxicity in veterinary patients after subcutaneous lidocaine injections for acquiring skin biopsy specimens. A recent report suggested that the total lidocaine volume administered in dogs should not exceed 11 mg/kg. In situations where higher dosages of lidocaine are needed (multiple skin biopsy sites per dog), the authors recommend using lower volumes of local anesthetics while performing skin biopsy under general anesthesia (RAINGER et al., 2009). However, the maximum

lidocaine dose of 11 mg/kg per dog was actually extrapolated from the convulsive toxic dose of intravenously administered lidocaine in conscious dogs (SKARDA, 1998), which does not equal subcutaneous administration, as the pharmacokinetics of lidocaine differ significantly depending on the route of administration (SCOTT et al., 1972). In this report, two dogs (dog 7 and 9) were administered a total lidocaine volume of more than 11 mg/kg with no adverse toxic side effects observed during 120 minutes post-administration.

There are some limitations to this study. First, sedative agents, such as α2-adrenergic agonis and, medetomidine, were used during skin biopsy procedures in some patients. This agent may potentiate the neurological effects of lidocaine, although supporting evidence is rare (RAINGER et al., 2009). No sedative agents were used in any dog during our study, which may lead to underestimating seizure occurrence in a clinical practice setting when medetomidine is additionally used for skin biopsy procedures. Second, only dogs with body mass greater than 5 kg were included in the study, so caution must be used when trying to extrapolate this lidocaine safety information for dogs with lower body mass (<5 kg).

In conclusion, subcutaneous administration of two different lidocaine local anesthetic formulations at 6 body sites per dog was shown to be well tolerated and safe in 9 dogs. Total lidocaine volume of up to 15 mg/kg subcutaneously injected did not cause any adverse toxic side effects, however, studies of its use for skin biopsies in dogs with lower body mass (<5 kg) and in conjunction with α2-adrenergic agonist medetomidine are needed to assess a lidocaine full toxicity panel. This research suggests that lidocaine and lidocaine/adrenaline formulation can be safely used as a local anesthetic for skin punch biopsies in dogs with body mass greater than 5 kg.

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SAŽETAK

Biopsija kože naširoko se primjenjuje kao dijagnostička metoda u veterinarskoj dermatologiji. Tijekom biopsije, potrebno je primijeniti lokalnu anesteziju i/ili sedaciju za sprečavanje boli. Lidokain je lokalni analgetik koji se često primjenjuje. Dodavanjem adrenalina uz lidokain pojačava se i produljuje analgetsko djelovanje. Intravenska primjena lidokaina u nekim je slučajevima pokazala značajne nuzučinke. Napadaj drhtavice smatra se najčešćim znakom intoksikacije, a bradiaritmija i smetnje u provođenju su rjeđe opisani nuzučinci. Cilj je ovog rada istražiti potencijalnu toksičnost lidokaina u dvije često primjenjivane lokalne anestezije: lidokain i lidokain/adrenalin kombinacija. Devet zdravih pasa nasumično su bili podijeljeni u dvije skupine. Jedna skupina (n = 4) primila je potkožne injekcije anestetika (ukupno šest injekcija od 1 mL s 2%-tnom lidokain otopinom), dok su psi u drugoj skupini (n = 5) primali lidokain/adrenalin kombinaciju (ukupno šest injekcija od 1 mL 2%-tnog lidokaina s 0,0125 mg adrenalin tartarata). Niti jedan od poznatih lidokainskih nuzučinaka nije zabilježen pri istraživanju. Koncentracija lidokaina u krvi daleko je ispod prijavljenog praga toksičnosti u pasa. Potkožna primjena dviju različitih anestetičkih formulacija pokazala se dobrom i sigurnom. Ovo istraživanje upućuje na zaključak da se lidokain i lidokain/adrenalin formulacije mogu sigurno primjenjivati kao lokalni anestetici pri biopsiji kože kod psa s tjelesnim težinama većim od 5 kilograma.

Ključne riječi: lidokain, adrenalin, toksičnost, biopsija kože, serumska koncetracija