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Intra-articular administration of lidocaine plus adrenaline in dogs: Pharmacokinetic profile and evaluation of toxicity in vivo and in vitro

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ABSTRACT

The aim of this study was to evaluate the safety of intra-articular (IA) lidocaine plus adrenaline for improving peri-operative analgesia in anaesthetized dogs undergoing arthroscopy of the elbow. A solution of lidocaine (L) 1.98% plus adrenaline 1:100.000 was administered via the IA route and its safety evaluated in terms of cardio-, neuro-, and chondro-toxicity.

No bradycardia or hypotension was recorded from induction to the last observational time point. Signs of toxicity of the nervous system could have been masked by the general anaesthesia but lidocaine concentrations detected in the blood were lower than those thought to be capable of producing toxicity. The assessment of in vitro chondrotoxicity showed a dose- and time-dependent effect of lidocaine on the viability of articular cells. Adrenaline appeared to reduce the chondrotoxicity of 1% lidocaine, following an exposure of up to 30 min.

Introduction

Arthroscopic surgery plays an important role in the treatment of various joint diseases in dogs (Miller and Beale, 2008; Bergenhuyzen et al., 2010) and the increasing use of the technique has highlighted the need to improve the quality of analgesia in the perioperative period. In humans undergoing arthroscopy, the relief of pain using intra-articular (IA) administration of α_2-agonists, opioids and local anaesthetics has been highly successful (Elhakim et al., 1999; Joshi et al., 2000). In particular, there are reports in the literature that effective analgesia follows an IA administration of lidocaine (Dahl et al., 1990; Arai et al., 2005).

Lidocaine is a local anaesthetic easily adsorbed from the injection site due to its chemical structure, has vasodilatory properties, and a pKa similar to the physiological pH (Schulman and Strichartz, 2012). Its absorption into the systemic circulation may cause cardiovascular and neurological toxic effects depending on the peak concentrations (Schulman and Strichartz, 2012). After IA administration of 2% lidocaine, Di Salvo et al. (2014) observed no signs of toxicity as regards the cardiovascular and nervous system but treated dogs were under anaesthesia, which could have masked the possible neurotoxic effects. These authors observed a rapid absorption of lidocaine from the joint and, in some dogs, the peak drug concentrations were higher than those considered by Lemo et al. (2007) to be responsible for neurotoxic effects in dogs (2.7 μg/mL). The addition of a vasoconstrictor such as adrenaline to a local anaesthetic reduces the local perfusion and generally decreases the absorption of the anaesthetic and the likelihood of reaching potentially toxic blood concentrations (Van Vynckt et al., 2010).

To the best of our knowledge, no studies on the safety of the IA administration of lidocaine plus adrenaline have been carried out during arthroscopic surgery in dogs. The purpose of this research was therefore to evaluate the absorption rate of lidocaine into the bloodstream after IA administration of a solution of lidocaine plus adrenaline in dogs undergoing arthroscopic surgery, in order to assess whether plasma concentrations potentially responsible for systemic toxicity would be reached. Moreover, since the use of local anaesthetics in humans by means of IA infusion pumps has been accompanied by severe cases of chondrolysis (Noyes et al., 2012) and we are unaware of any studies on the effect of lidocaine on the cells of canine cartilage, the possible toxic effects of lidocaine and lidocaine plus adrenaline on chondrocytes were also examined.

Material and methods

The study was approved by the Bioethical Committee of the University of Perugia (number 2012-039; 5 October 2012), and the owners, who had all been appropriately informed about the aims and modalities of the study, provided their written consent.

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Table 1
Age, weights, sex, articular pathology, degree of inflammation of recruited animals and pharmacological treatments.

Age (months)	Weight (kg)	Sex	Disease	Score attributed to lesion	Treatment	mL admin.	Dose (mg/kg)	*n* Sufentanil boluses *
10	31.5	M	FCP	3	Lidocaine + adrenaline	15	9.43	0
84	37.1	M	DJD	1	Lidocaine + adrenaline	12	6.40	3
24	56.4	M	ED	2	Lidocaine + adrenaline	20	7.02	1
12	31.7	M	FCP	2	Lidocaine + adrenaline	12	7.50	0
9	29.7	F	FCP	2	Lidocaine + adrenaline	13	8.67	0
18	28.7	M	MCD	2	Lidocaine + adrenaline	12	8.28	1
6	27	M	OCD	2	Saline	15		1 + CRI
11	33	M	OCD	1	Saline	15		3
12	38	F	FCP	3	Saline	18		0
24	57	M	OCD	2	Saline	20		1
84	37.5	M	FCP	1	Saline	9		4
30	34	M	FCP	3	Saline	10		1

FCP, fragmented coronoid process; DJD, degenerative joint disease; ED, elbow dysplasia; MCD, medial compartment disease; OCD, osteochondritis dissecans; 1, low; 2, moderate; 3, high; F, female; M, male; CRI, continuous rate infusion(0.5 μg/kg).
* 0.1 μg/kg as rescue analgesia.

Treatments and clinical evaluations of animals

Twelve dogs admitted to the Veterinary Teaching Hospital of the University of Perugia for an elbow arthroscopic surgery were considered as eligible subjects for the study. All animals were healthy and classified as ASA I or II. The degree of inflammation was established by clinical and radiographic orthopaedic assessment, and a scoring scale from 1 to 4 (1 = low; 2 = low/moderate; 3 = moderate/high; 4 = severe) was applied to determine the severity of the joint disease. Dogs with significant capsular swelling related to severe and extensive synovitis (degree 4) were not included in this study. The weight, age and degree of joint inflammation of the recruited animals are summarized in Table 1.

A fresh solution of lidocaine plus adrenaline was prepared by adding 200 μL of a solution containing adrenaline (1 mg/mL) (Adrenalina Monico Spa) to 19.8 mL of 2% lidocaine (Lidocaine Hydrochloride, SALF.). The final solution contained 1.98% lidocaine plus 1:100,000 adrenaline (pH 7.0).

As a pre-emptive analgesic treatment, dogs received 0.1 mg/kg of meloxicam for at least 3 days before surgery. Prior to arthroscopy, dogs were premedicated with 10 μg/kg of acepromazine (Prequillan, Fatro) by the intramuscular route, then general anaesthesia was induced with 4–6 mg/kg of propofol (Proposure, Merial) and maintained by a mixture of isoflurane (Isoflo; Esteve Spa) and oxygen (50–100 mL/kg/min). Subsequently, dogs were randomly assigned to one of the following two experimental groups. Group LA (six subjects) received the solution of lidocaine plus adrenaline, and Group S (six subjects) received 0.9% saline.

In order to assure a sufficient joint distension (necessary to minimize the trauma during the establishment of the arthroscope portal), in both groups the solutions were injected until the surgeon perceived a counter pressure on the plunger of the syringe. Thus, different volumes of the lidocaine-adrenaline solution and variable doses of lidocaine were injected in each joint. A volumetric limit was established at 10 mg/kg of lidocaine, which is the maximum therapeutic dose considered safe for regional and local anaesthesia (Lemo et al., 2007). Table 1 summarizes the injected volumes and the total doses of lidocaine administered to each dog.

The arthroscopic procedure began 15 min after the injection and the joint was continuously flushed with Ringer lactate throughout the procedure. Immediately after the induction of anaesthesia, and up to recovery, clinical parameters, namely, heart rate (HR), electrocardiogram (ECG), respiratory rate (RR), non-invasive systolic (SAP), diastolic (DAP) and mean arterial blood pressure (MAP), haemoglobin oxygen saturation, end-tidal carbon dioxide partial pressure, isoflurane exhaled concentration and rectal temperature (T°), were continuously monitored by a Multi-Parameter Monitor (HB100; Foschi).

If an increase in HR, blood pressure or RR (>20% compared with baseline) was observed, one or more intravenous (IV) boluses of sufentanil (0.1 μg/kg, Sufentanil-hameln, Hospira) were administered as rescue analgesia. The value recorded at the steady state of anaesthesia just before surgical procedures was used as the baseline measurement. To assure an adequate postoperative analgesia, 0.1 mg/kg of meloxicam (Metacam, Boehringer Ingelheim) was administered subcutaneously at the end of anaesthesia.

At predetermined time-points during the post-surgical period, up to discharge, ECG, HR, RR, SAP, DAP, MAP and T° were monitored and dogs were evaluated for the presence of pain by mean of the numeric rating scale of Hellyer and Gaynor (1998), slightly modified. If deemed necessary, 10 μg/kg of buprenorphine was administered IV as rescue analgesia.

Blood sampling

At scheduled time points (0, before; then 5, 10, 15, 30, 60, 90, 120, 180, 240 and 360 min after the IA administration of lidocaine plus adrenaline), blood samples were taken from the dogs of the LA group in order to determine the serum concentrations of lidocaine and its active metabolite monoethylglycinexylidide (MEGX).

Analytical determination of lidocaine and MEGX

Stock solutions (1 mg/mL) of lidocaine hydrochloride monohydrate (Dr Ehrenstorfer), MEGX (Sigma Aldrich) and lidocaine HCl d10 (internal standard, CDN Isotopes) were prepared in methanol and stored at –20 °C.

Serum samples (100 μL) were added to 100 μL of internal standard and 800 μL of acetonitrile, vortexed and then centrifuged at 18,000 *g* for 5 min. Organic layers (100 μL) were diluted with 400 μL of acetonitrile and 10 μL was injected in the LC-system. Quantitative analyses were conducted by means of a triple quadrupole mass spectrometer (TSQ Quantum Ultra, Thermo Fisher) equipped with a LC- system (Finnigan Surveyor LC pump, Thermo Fisher) via electrospray ionization (ESI) interface. The chromatographic analytical column was a BetaBasic-18 (150 mm × 2.1 mm, 5 μm, Thermo Electron Corporation). The separation was performed in gradient mode, using as mobile phases water and acetonitrile, both containing 0.1% (V/V) formic acid; the flow rate was 0.3 mL/min. The ESI source operated in positive ion mode. The parameters were as follows: spray voltage 3.5 kV and capillary temperature 270 °C. The concentration of lidocaine or MEGX was determined by the internal standard method.

In vitro evaluation of chondrotoxicity

Canine chondrocytes were isolated from the cartilage harvested from the knee joints of a dog which had been euthanased for reasons unrelated to the present study. Primary cultures of canine chondrocytes were prepared and used to assess the cell viability following exposure to different concentrations of lidocaine alone at 0.5, 1 and 1.98% (L) and lidocaine (same concentrations) plus adrenaline 1:100,000 (L+A). In a pilot study, the effects of chondrocyte exposure to adrenaline alone (10 μg/mL) were also tested and no significant reduction in cell viability was observed (data not shown).

Cartilage slices were rinsed in Dulbecco's phosphate-buffered saline (DPBS), minced and digested primarily with 0.25% trypsin for 10 min at 37 °C and subsequently with 2 mg/mL collagenase type IA (Sigma-Aldrich) at 37 °C for 10/12 h. The cells were cultured in a Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum, penicillin (100 U/mL) and streptomycin (100 μg/mL) in 5% CO_2 at 37 °C in a humidified atmosphere. Cell viability was assessed by measuring the conversion of tetrazolium salt (WST-8) to a water-soluble formazan dye using a cell counting kit-8 (CCK-8; Dojindo) according to the manufacturer's instructions.

Cells were exposed for 10, 15, 30 and 60 min to L and L+A at the above reported concentrations. DPBS was used as a solvent to prepare dilution and as a control medium. The effect of drugs on cell viability was expressed as the WTS-8 percentage reduction in treated cells compared to the controls, assuming the absorbance of control cells was 100% ($A_{(treated\ cells)}/A_{(control)} \times 100$). Data were obtained from four independent experiments, which were performed in triplicate and expressed as the mean ± standard deviation (SD).

Statistics and pharmacokinetic analysis

The homogeneity of the groups as regards age, sex, weight and degree of lesion was evaluated by the Mann–Whitney test, whereas the correlation between the maximum serum concentrations and the volume of the injected solution, the dose and the degree of lesion was performed by Spearman's rank correlation. The statistical significance of changes in chondrocyte viability was determined by a one-way analysis of variance (ANOVA), followed by Bonferroni's post hoc test. For all tests