Serum lidocaine concentration after epidural administration in dogs

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ABSTRACT: The pharmacokinetics of lidocaine deals with the measurement of lidocaine concentration in the blood and its changes over time. The toxicity of lidocaine is a function of its peak plasma concentration, which in turn depends on several factors including total dose and rates of systemic absorption and elimination. The aim of the study was to assess serum levels of lidocaine after a single shot epidural injection in dogs seen in daily practice. The study included nine dogs undergoing different types of surgery. The animals were anesthetized with a combination of diazepam and ketamine; then lidocaine was injected epidurally. Blood samples for measurement of serum lidocaine concentration were obtained before and at 10, 30, 60 and 120 min after single injection. Basic vital parameters of heart rate, respiratory rate, mean arterial pressure and hemoglobin saturation were recorded before induction of general anesthesia (T_1), immediately after intubation (T_2), and then at 10, 30, 60 and 120 min of epidural lidocaine administration. Study results indicated that serum lidocaine concentration did not reach the levels of potential toxicity in dogs upon epidural injection of 4 mg/kg lidocaine at a concentration of 2% and there were no significant alterations in basic vital parameters.

Keywords: epidural anesthesia; lidocaine; dog

Epidural anesthesia is well recognized as one of the most frequently used regional anesthetic techniques in veterinary practice. It is useful in caudal surgery as well as in caudal abdominal and/or perineal region (Pascoe, 1992; Rauser et al., 2004). A previous clinical trial has indicated that epidural anesthesia used in combination with light general anesthesia might reduce the rate of postoperative complications (Yeager et al., 1987). Lidocaine is the epidural anesthetic most frequently used in practice, yet bupivacaine is also used (Skarda, 1998). One of the potential problems during epidural anesthesia is local anesthetic toxicity, which may occur either because of an excessive amount of the drug administered extravascularly or because of accidental intravascular injection.

The pharmacokinetics of lidocaine deals with the measurement of lidocaine concentration in the blood and its changes over time. The toxicity of lidocaine is a function of its peak plasma concentration, which in turn depends on several factors including total dose and rates of systemic absorption and elimination. Lidocaine can be toxic if its concentration in the blood exceeds a threshold of 5 µg/ml (Savarese and Covino, 1986). We therefore decided to determine serum levels of lidocaine after a single shot epidural injection in dogs seen in daily veterinary practice.

MATERIAL AND METHODS

The study included nine dogs of both sexes, mean age 7.7 ± 3.5 years, mean weight 25.6 ± 11.3 kg, hospitalized at Department of Surgery for minor lower abdominal or extremity surgery. Study protocol was approved by the Research Committee of the University Department of Surgery, Orthopedics and Ophthalmology, Faculty of Veterinary Medicine, University of Zagreb, and followed the national legislature on care and use of laboratory animals. An informed consent was obtained from all dog owners.

Food and water were withheld for 12 hours before the study. The animals received no premedication. Cephalic vein was catheterized for blood sampling, and an intravenous catheter was inserted for infusion of lactated Ringer's solution *via* cephalic vein from the contralateral limb. Upon establishment of *i.v.* route, anesthesia was induced with a combination of diazepam 0.25 mg/kg (Apaurin, Krka, Slovenia) and ketamine 10 mg/kg (Narketan, Chassot, Germany). Upon endotracheal intubation, dogs were connected to anesthetic machine and maintained on spontaneous ventilation. Anesthesia was maintained with 1.5% isoflurane in oxygen and lactated Ringer's solution was infused at a rate of 10 ml/kg/h (Infusion pump BIOF 3000, Biotron CO, South Corea) during surgical procedure. Cefuroxime 22 mg/kg *i.v.* (Ketocef, Pliva, Croatia) was administered for preoperative antibiotic prophylaxis.

Then, the dogs were placed in the left lateral position and hind limbs were flexed to maximally separate lumbar vertebrae. Epidural anesthesia was administered aseptically. The lumbosacral region (L_7–S_1) was shaved and surgically prepared with povidone iodide. A sterile Tuhoy needle was inserted into epidural space at L_7–S_1 interspaces. The needle gage depended on the dog size (20 to 22 gages). The epidural space was identified by the loss-of-resistance technique to the injection of 2 ml of air after piercing the arcuate ligament. A 5-ml syringe was attached to the needle and aspiration was applied to confirm correct needle placement and to detect accidental intravascular or subarachnoid needle placement. Lidocaine 2% (Lidokain 2%, Belupo, Croatia) was then administered in a dose of 1 ml/5 kg (4 mg/kg) over 50 seconds. The effect of epidural anesthesia was controlled by observing dilatation of the external sphincter, followed by relaxation of the tail. Venous blood samples for lidocaine concentration measurement were drawn by the syringe at 10, 30, 60 and 120 min after single epidural administration. Blood samples were collected in sterile glass tubes containing no anticoagulant. Within 2 hours of blood collection, serum was separated by centrifugation. After centrifugation, a minimum of 1 ml of serum was stored in a polypropylene vial and frozen at –70°C until assayed. The serum concentration of lidocaine was determined by chromatography and mass spectrometry on a Hewlett Packard 6890 and 5973 GC-MS system (Hewlett Packard, CA, USA). This method for lidocaine assay is accurate, highly specific and precise. The limit of quantification was 50 ng/ml. The inter- and intra-assay coefficient of variation was < 10%.

Heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP) and hemoglobin saturation with oxygen (SpO_2) were monitored and measured preoperatively (T_1), immediately after intubation (T_2), and then at 10, 30, 60 and 120 min after single shot epidural injection of lidocaine.

Lead II electrocardiograph was used to record heart rate and capnograph (mainstream technique) was used to determine respiratory rate. A digital electronic blood pressure device with pediatric cuff wrapped around the dog's metatarsus was used to measure arterial blood pressure. Hemoglobin saturation with oxygen was determined by pulse oxymetry from a sensor placed on the tip of the tongue. Measurements were done on an anesthetic monitor (Ultraview 1050, Spacelabs, USA).

Data were entered in tables and expressed as mean and standard deviation. The analysis of variance was used on data testing for difference significance. For statistical evaluation, Student's *t*-test was used. Results were considered statistically significant at $P < 0.05$.

RESULTS

Dog characteristics and type of operation are shown in Table 1. Adequate surgical anesthesia was achieved during the operation and dogs woke up free from pain. There was no evidence of systemic local anesthetic toxicity in any dog. As shown in Table 2, epidural administration of lidocaine produced no significant alterations in HR, RR, MAP and SpO_2.

In the majority of study dogs, serum concentration of lidocaine increased 10 min after epidural

Table 1. Patient characteristic

Breed	Sex	Age (year)	Weight (kg)	Diagnosis	Surgery
Mixed	m	12	13	perianal adenoma	orchiectomy, surgical excision of tumor
German Shorthaired Pointer	f	11	29	mammary gland tumor	regional mastectomy
Labrador Retriever	m	6	39	cranial cruciate ligament rupture	extracapsular reconstruction
Rotweiller	f	3	35	constipatio	laparotomy and colotomy
Standard Schnauzer	m	4	21	nail bed carcinoma	digital amputation
Boxer	m	8	33	preaputial neoplasia	surgical excision of tumor
Mixed	f	13	14	bite wound	tail amputation
Rotweiller	f	5	37	metatarsal fractures	osteosynthesis
Mixed	m	8	10	kryptorchismus and testicular neoplasia	laparotomy and orchiectomy

Table 2. Effects of epidural administration of lidocaine on HR, MAP, RR and SpO_2 in dogs (n = 9). Values presented as mean ± standard deviation (SD)

Variables	Time after treatment					
	T_1	T_2	10	30	60	120
HR (beats/min)	88.2 ± 8.5	85.3 ± 7.5	85.9 ± 6.0	86.8 ± 4.31	87.4 ± 5.4	89.8 ± 6.4
MAP (mmHg)	93.6 ± 6.3	89.6 ± 5.6	90.6 ± 2.8	92.7 ± 6.0	92.1 ± 4.04	93.4 ± 3.4
RR (breaths/min)	19.7 ± 1.5	18.6 ± 1.2	19.1 ± 0.9	18.7 ± 0.8	19.3 ± 0.7	19.7 ± 1.2
SpO_2 (%)	99.2 ± 0.6	99.5 ± 0.5	99.3 ± 0.7	99.5 ± 0.5	99.4 ± 0.7	99.0 ± 0.7

administration, and then decreased steeply over the next 120 min (Table 3). The mean serum concentration of lidocaine was 2.6 ± 0.89 μg/ml at 10 min, 2.48 ± 0.87 μg/ml at 30 min, 2.08 ± 0.69 μg/ml at 60 min, and 1.39 ± 0.41 μg/ml at 120 min. The individual peak serum concentration (C_{max}) in all dogs ranged between 1.5 and 4.31 μg/ml, with a mean of 2.86 ± 0.96 μg/ml. In most dogs, C_{max} was achieved 10 min after lidocaine administration. In two dogs, C_{max} was achieved 30 min after epidural injection. The highest serum concentration of lidocaine (4.31 μg/ml) was recorded in dog No. 9.

Table 3. Serum lidocaine concentration (μg/ml) at different time following epidural administration of lidocaine

Patient No.	Time interval (min)			
	10	30	60	120
1	2.38	2.11	1.63	1.1
2	1.50	1.45	1.48	1.06
3	2.19	3.06	2.02	1.27
4	3.20	2.23	2.07	1.27
5	3.37	2.54	2.47	1.70
6	3.29	3.97	3.19	1.64
7	1.90	1.56	1.44	1.08
8	2.07	1.89	1.35	1.12
9	4.31	3.56	3.09	2.31

DISCUSSION

The study was performed to determine serum concentration of lidocaine and associated changes

in vital parameters after a single shot epidural injection. It is well known that epidural anesthesia, when properly performed and with appropriate concentration of local anesthetic used, usually does not result in blood levels of local anesthetic that may cause systemic toxicity. Systemic toxicity can occur as the result of intravascular injection or administration of an excessive dose of local anesthetic into the epidural space. The risk of toxicity depends on the peak concentration of lidocaine. Lower peak plasma lidocaine concentrations reduce the risk of lidocaine toxicity. Systemic toxicity primarily involves the central nervous system and cardiovascular system (Liu et al., 1982, 1983; Groban, 2003). The cardiovascular system is more resistant to local anesthetics than the central nervous system. The dose and blood level of local anesthetic required to produce cardiovascular toxicity were usually four to seven times greater than the dose of local anesthetic necessary to produce neurologic side effects (Liu et al., 1983). Hemodynamic studies in anesthetized dogs showed that lidocaine caused a 50% decrease in cardiac output at doses of 30–40 mg/kg. Lidocaine in a dose of 10 mg/kg produced moderate change in cardiovascular function, and minimal changes were observed with doses of 0.3–3 mg/kg (Liu et al., 1982).

Lidocaine produced biphasic effects on the cardiovascular system. Bonica et al. (1971) found the blood levels of lidocaine of less than 4 μg/ml following epidural anesthesia to produce a slight blood pressure elevation due to the increased cardiac output. Doses of epidural lidocaine that produced higher concentrations of lidocaine (> 4 μg/ml) caused hypotension due to its ability to produce peripheral vasodilation. In our study, we used 4 mg/kg of lidocaine, individual peak serum concentration (C_{max}) ranged between 1.5 and 4.31 μg/ml, with a mean of 2.86 ± 0.96 μg/ml, and no changes in heart rate and blood pressure were observed. These findings are consistent with the data reported by Peters et al. (1991) and Rauser et al. (2004), who observed no significant HR and MAP alteration after epidural administration of lidocaine in dogs either.

The central nervous system is more sensitive to local anesthetic than the cardiovascular system. Neurologic complications that may occur after induction of epidural anesthesia include Horner syndrome, Schiff-Sherrington-like reflex, and signs associated with local anesthetic toxicity such as muscle twitch, coma and convulsion (Jones, 2001). Savarese and Covino (1986) report on the central nervous system toxicity to develop when lidocaine concentration exceeds 5 μg/ml. Feldman et al. (1989) evaluated systemic toxicity, arrhythmogenicity, and mode of death associated with convulsant and supraconvulsant doses of lidocaine, bupivacaine, and ropivacaine in dogs. They showed that the average dose and plasma level of lidocaine at the onset of convulsion were 20.8 ± 4.0 mg/kg and 47.2 ± 5.4 μg/ml, respectively. In our study, none of the dogs reached toxic level, and the blood concentration of lidocaine was far below the convulsive threshold. The highest serum concentration of lidocaine was 4.31 μg/ml. It should be noted that we observed no type of neurologic toxicity; however, epidural anesthesia was performed under general anesthesia, so neurologic signs of toxicity would have been masked by the loss of consciousness.

Pharmacokinetic studies have reported that the maximum concentration of lidocaine after epidural administration occurs in some 10 min (Doherty et al., 1996; Yokoyama et al., 1998). Doherty et al. (1996) report that the median time to reach maximal plasma concentration of 2% lidocaine was 10.7 min after single shot epidural injection, and the C_{max} value of lidocaine was 2.23 μg/ml. This finding is in accord with our data. In our study, the time to maximal serum concentration of lidocaine was 10–30 min. In most dogs it was 10 min after the administration of lidocaine, and in only two dogs C_{max} was achieved 30 min after epidural injection.

Accordingly, the serum concentration of lidocaine following epidural administration of 4 mg/kg lidocaine at a concentration of 2% does not appear to be associated with potential toxicity, suggesting that epidural anesthesia with lidocaine is a safe procedure in dogs.

The small number of dogs included in the study precluded any definite conclusions to make, however, additional studies of the potential toxicity and pharmacokinetics of lidocaine may hopefully provide definite answers.

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