



Evaluation of Intravenous Lidocaine Overdose in Chickens (*Gallus domesticus*)

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Abstract

Objective- To evaluate the total toxic dose of lidocaine and serum lidocaine concentrations resulting in clinical signs of toxicity in chickens.

Design- Experimental study

Animals- Eight healthy, female, 55-week-old chickens (Lohman breed) weighing 1.45 ± 0.17 kg (mean \pm SD)

Procedure- A loading dose of 2% lidocaine (4 mg/kg) was administered IV, followed by a constant-rate infusion at a dose of 8 mg/kg/min using a syringe pump. Times to onset of convulsion and/or respiratory arrest were recorded and the total toxic dose of lidocaine was determined. Blood sample was withdrawn for lidocaine analysis at the onset of the major signs of intoxication (convulsion or respiratory arrest).

Results- The total toxic dose of lidocaine required to produce systemic toxicity and corresponding serum lidocaine concentration were 28.96 ± 6.21 mg/kg and 38.5 ± 10.4 μ g/mL, respectively.

Conclusions and clinical relevance- Based on the results of this study, greater doses of lidocaine are needed to produce toxic manifestations in chickens as compared with mammals.

Key words- Lidocaine, Infusion, Toxicity, Chicken.

Introduction

Local analgesic techniques are commonly used to provide perioperative analgesia, reducing both general anesthetic and systemic analgesic requirements.¹ Local anesthetic drugs exert their nerve blocking effect by binding to sodium channels, thus causing the interruption of the axonal action potential propagation.² The same mechanism is also responsible for central nervous system and cardiovascular toxicity.

Unlike all other drugs in anesthesia, local anesthetic drugs are injected at their site of action, where the drug concentration is many times higher than is found in arterial blood after absorption. As local anesthetics are absorbed from the injection site, their systemic serum concentration rises and the central nervous system and cardiovascular system are affected in a dose-dependent manner.² Systemic toxicity is seen most commonly following inadvertent intravascular injection or drug overdose. As expected, the serum

concentration is directly related to the dose and speed of injection.

Although several studies have described local anesthetic techniques in birds,³⁻⁷ local anesthetics are not commonly used in birds due to alleged higher susceptibility to local anesthetic toxicity.⁸⁻¹¹

Lidocaine is the most commonly used local anesthetic to perform neuraxial and peripheral nerve blocks because of its fast onset and intermediate duration of action. Systemic toxicity following administration of lidocaine and bupivacaine has been reported previously in humans,¹² dogs,¹³⁻¹⁵ cats,¹⁶⁻¹⁸ horses¹⁹ and sheep.²⁰⁻²² Toxic effects of local anesthetics in birds were reported with lower doses and are similar to those were seen in mammals, including muscle tremors, ataxia, convulsion, drowsiness, recumbency, cardiac arrest and death.^{9,10}

The purpose of this study was to identify toxic dose of lidocaine and determine blood serum lidocaine concentrations in the chicken resulting in clinical signs of toxicity associated with intravascular administration.

Materials and methods

Eight healthy, female, 55-week-old chickens (Lohman breed) weighing 1.45 ± 0.17 kg (mean \pm SD) were used. These birds were obtained from the chicken's farm of Veterinary Faculty,

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Shiraz University, Shiraz, Iran. Birds were free of disease and had been vaccinated against Gamboro and Marek's diseases. Health status was established on the basis of a thorough physical examination. All birds were housed in a controlled environment (16 h light/ 8 h dark photoperiod, 20-25 °C) with free access to water and food (balanced bird ration). They were acclimatized for 2 weeks prior to onset of this study. Birds were not fasted before the administration of medication. All experiments were conducted in the morning (9.00-12.00). The Institutional Animal Care and Use Committee approved the protocol of this project.

To conduct the experiment, each bird was gently restrained in dorsal recumbency and two 22 gauge intravenous (IV) catheters were placed into the right brachial vein and right metatarsal vein for drug injection and blood sample collection, respectively. A loading dose of 2% lidocaine (4 mg/kg, lidocaine hydrochloride, Sina Darou, Tehran, Iran) was administered IV by slow bolus injection (over a 30 seconds period) into the right brachial vein, followed by a constant-rate infusion at a dose of 8 mg/kg/min using a syringe pump (SP-100; JMS, Japan) until clinical signs of toxicity (convulsion and/or respiratory arrest) were observed. Lead II of the ECG (Cardiostat 701, Simens, Germany; paper speed 50 mm/sec, sensitivity 20 mm/mV) was recorded continuously before and during lidocaine infusion.

During infusion period, the bird was closely monitored for signs of lidocaine toxicity. Based on the pilot study performed in 6 chickens, the first toxic manifestations which appeared during the lidocaine infusion in experimental chickens were panting, followed by convulsion and/or respiratory arrest. Panting was described as rapid, shallow, open-mouth respiration and tongue movement. Convulsion was defined as loss of consciousness, a continuous twitching of head and neck and jaw chomping. Respiratory arrest was defined as apnea lasting longer than 20 seconds. Following observation of either convulsion or respiratory arrest (whichever occurred earlier), infusion of lidocaine was discontinued immediately, the duration of infusion was recorded and blood sample (2 mL/sample) was collected for lidocaine analysis from the right metatarsal vein in sterile glass blood collection tubes containing no anticoagulant agent. Blood samples were centrifuged (3000 rpm for 10 min) and serum was separated and frozen at -20 °C until analysis. The total dose of lidocaine was calculated for each bird.

A modification of previously described method of high performance liquid chromatography (HPLC) was used to determine the serum concentration of lidocaine in chickens.²³ The mobile phase was consisted of sodium dihydrogen phosphate buffer (pH was adjusted to 4 with phosphoric acid and sodium hydroxide) and acetonitrile (25:75, v/v) which was pumped at a flow rate of 0.9 mL/min. To generate standard curve, seven different concentration of lidocaine (1, 2, 5, 10, 20, 50, 100 µg/mL) was prepared in methanol. Then 100 µL of each concentration of lidocaine, 100 µL bupivacaine (100 µg/mL in water), 200 µL pure chicken serum, 2 mL water and 2 mL acetonitrile were mixed and vigorously vortexed. After centrifugation (2500 rpm, 20 min) supernatant was transferred to a clean tube and mixed with 6 mL n-Hexane and 0.5 mL

sodium hydroxide. The mixture was vortexed and centrifuged (2500 rpm, 15 min) again. Extraction was evaporated to dryness under a gentle stream of nitrogen at room temperature (25 °C). The residue was reconstituted in 120 µL mobile phase and was vortexed for 30s. At the end, 20 µL of final mixture was injected to HPLC system. Sample's preparation was similar except for adding various concentration of lidocaine.

The Knauer HPLC system (Knauer, Germany) employed consisted of a Smartline Pump 1000 (Knauer, Germany), Rheodyne-Ventil RH7725i Sample Injector (Rheodyne, USA) and Smartline UV Detector 2500 (Knauer, Germany). Separation was performed by an analytical MZ-Analysentechnik (150 × 4.0 mm, 35 µm particle size) column. The wavelength was set at 210 nm. The detection limit of lidocaine was 0.1 µg/mL.

Statistical analysis was performed using SPSS version 11.5 for Windows (SPSS, MicroMaster, Richboro, PA, USA). Mean ± SD values were determined for time to onset of panting, convulsion and respiratory arrest, and the serum lidocaine concentrations during convulsion and respiratory arrest. A one way ANOVA followed by Duncan's test was utilized to compare the doses of lidocaine required to induce panting, convulsion or respiratory arrest. The data for serum concentrations of lidocaine during convulsion or respiratory arrest were compared using student's t-test. Differences were considered significant at $p < 0.05$.

Results

The frequency and sequence of symptoms of lidocaine toxicity are presented in Table 1. Panting was observed at 2.1±0.7 min after starting the lidocaine infusion in 6 birds. Significantly ($p < 0.05$) longer time was required to observe convulsion (4.76 ± 0.45 min) or respiratory arrest (4.16 ± 0.97 min). The doses of lidocaine required to induce panting, convulsion and respiratory arrest were 16.02 ± 5.13, 30.86 ± 6.26, and 27.06 ± 6.42 mg/kg, respectively (Table 2).

In three cases respiratory arrest was observed first, followed within seconds by convulsion and in one case respiratory arrest occurred following convulsion. One chicken progressed directly to respiratory arrest without evidence of convulsion. All birds showing convulsion without respiratory arrest were recovered spontaneously without any adverse sequelae. Overall, respiratory arrest occurred in 5 birds. Two birds recovered spontaneously and resuscitation (opening the mouth, oxygen administration and intermittent compression of the chest) was performed in 3 other cases. Resuscitation was successful in one bird and death occurred due to cardiopulmonary collapse in the remaining two birds. In all chickens, heart sound was audible on auscultation during convulsion, respiratory arrest and resuscitation period.

Corresponding lidocaine serum concentrations during convulsion (36.8 ± 8.4 µg/mL) and respiratory arrest (40.2 ± 13.3 µg/mL) were not significantly different ($p > 0.05$) (Table 2). Overall, total lidocaine dose and serum lidocaine concentration required to induce either convulsion or respiratory arrest were 28.96 ± 6.21 mg/kg and 38.5 ± 10.4

µg/mL, respectively. Heart rate slightly decreased after bolus lidocaine administration (324 ± 31 vs. 315 ± 26 beats/min) but significant reduction (243 ± 30 beats/min) was observed following lidocaine infusion. No other significant arrhythmias

were observed during infusion of lidocaine. Ventricular fibrillation and cardiac asystole were the terminal electrocardiographic findings of lethal lidocaine intoxication (Fig.1).

Table 1- Frequency and sequence of toxic manifestations following administration of lidocaine overdoses in 8 chickens

No.	Panting	Convulsion	Respiratory arrest	Death
1	-	+ ^a	-	-
2	-	+ ^a	-	-
3	+ ^a	+ ^b	+ ^c	+
4	+ ^a	-	+ ^b	-
5	+ ^a	+ ^c	+ ^b	R
6	+ ^a	+ ^c	+ ^b	+
7	+ ^a	+ ^b	-	-
8	+ ^a	+ ^c	+ ^b	-

a, b, c, first, second and third manifestations; R, successful resuscitation

Table 2- Individual and mean (± SD) dose of lidocaine (mg/kg) required to produce each toxic manifestation and individual and mean (± SD) serum concentration (µg/mL) at onset of convulsion and/or respiratory arrest.

	Bird number								Mean ± SD
	1	2	3	4	5	6	7	8	
<u>Dose Administered (mg/kg)</u>									
Panting (n=6)	-	-	11.1	16.9	15.2	16.6	25.1	11.3	16.0 ± 5.1 *
Convulsion (n=4)	24.3	35.6	26.7				36.76		30.9 ± 6.3
Respiratory arrest (n=4)	-	-	-	19.1	26.6	34.8	-	27.69	27.1 ± 6.4
<u>Serum concentration (µg/mL)</u>									
Convulsion (n=4)	48.5	31.7	29.9	-	-	-	37.2	-	36.8 ± 8.4
Respiratory arrest (n=4)	-	-	-	21.0	42.0	48.0	-	49.9	40.2 ± 13.3

* Significantly different from convulsion and respiratory arrest values (p < 0.05).

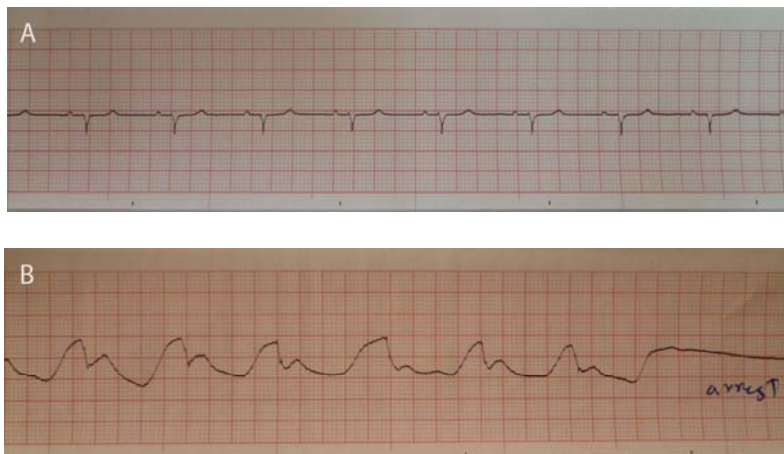


Figure 1- Electrocardiographic findings during lidocaine infusion (8 mg/kg/min) in chickens. A: Bradycardia. B: Ventricular fibrillation and cardiac asystole.

Discussion

In avian species, local anesthetics are most often used in topical applications for minor procedures (catheter placement, endotracheal intubation), local infiltration at the surgical site (placement of air sac tubes, intraosseous catheters, laparotomy), and local nerve block. Local anesthetic techniques have also been used in combination with general anesthesia in the avian species.^{24,25}

Lidocaine is a commonly used local anesthetic agent with broad applications including local infiltration, regional nerve blocks, epidural and spinal anesthesia. Lidocaine is especially popular in veterinary medicine given its fast onset of action, intermediate duration of action and its low incidence of adverse reactions.¹

Information about local anesthetic toxicity in birds is limited and the relative toxicity and the margin of safety of local anesthetics are unknown. Although no study on toxic effect of lidocaine has been reported in birds, it is generally recommended that the dose of lidocaine should be kept below 4 mg/kg.^{10,26}

Birds are believed to be more sensitive to the effects of local anesthetics than mammals. Toxicity has been observed in birds at lower doses of bupivacaine (2.7 to 3.3 mg/kg) than in dogs.⁴ However, a relatively high doses of lidocaine (15 and 20 mg/kg), bupivacaine (5 and 8 mg/kg) and ropivacaine (7.5 mg/kg) have been used for brachial plexus block in chickens and mallard duck without any adverse effects.⁵⁻⁷ The doses of lidocaine used in these studies were much higher than the maximum recommended dose of 4.0 mg/kg.²⁷ It has been suggested that the higher risk of local anesthetic toxicity in birds may be simply related to the small size of some avian species and inappropriate doses.²⁷

The study reported here determined toxic dose as well as serum concentration of lidocaine following continuous infusion of high doses of lidocaine in chicken. In order to approximate the worst possible clinical scenario of inadvertent intravenous injection, a relatively rapid intravenous infusion rate (8 mg/kg/min) was administered immediately following a bolus injection of 4 mg/kg and the first occurrence of convulsion or apnea was taken as the CNS toxic end point and the infusion was discontinued.

Total doses of lidocaine ranging from 5.8 to 11.7 mg/kg have been reported to produce convulsion in sheep, cats, horses and dogs.^{17,19,28,29} In our study, convulsive dose of lidocaine in chickens was 30.51 ± 5.15 mg/kg which is the highest dose among all species. The blood concentrations necessary to produce convulsion are 1.56-2.7 µg/mL in dogs, 8.21 µg/mL in humans, 11.7 µg/mL in sheep, and 19.6 µg/mL in cats.^{15,19,28-30} Meyer et al (2001) reported the convulsive blood concentration of lidocaine at 1.85-4.53 µg/mL in horses.¹⁹ In the present study serum concentration that produced convulsion in chickens was 39.52 ± 10.8 µg/mL. In the present study, apneic and convulsant doses of lidocaine were close to a lethal dose. A narrow margin between convulsant and lethal doses of local anesthetics has been reported in spontaneously breathing mice.³¹ Respiratory arrest is thought to be the precipitating cause of lidocaine-induced death in

chickens; however, a direct myocardial effect of the local anesthetic cannot be ruled out.

Central nervous system (CNS) and cardiovascular system (CVS) are two main systems involved in local anesthetic toxicity. Central nervous system toxicity typically occurs more frequently and at lower serum concentrations of local anesthetics than those required to cause cardiovascular toxicity.¹ It has been reported that local anesthetics have a biphasic effect on the CNS in which inhibitory pathways are blocked first leading to excitatory phenomena including convulsion. With higher plasma concentration, all neurons are blocked resulting in severe CNS depression, respiratory arrest and coma.³² In the present study, convulsion, respiratory arrest and death occurred at a similar serum concentration. Two out of five birds with lidocaine-induced respiratory arrest died, while both two birds with convulsion alone survived. It has been reported that cats can survive at least 2 times the convulsant dose of lidocaine, providing respiration and circulation are maintained.¹⁸ In sheep, significantly lower doses and blood levels of lidocaine were required to produce convulsive activity as compared to the doses and blood levels determined at the onset of respiratory arrest and circulatory collapse.²⁸ This difference may be due to the different anatomical structure and physiological function of chicken's brain. It has been reported that the avian blood brain barrier is not as highly structured as that of mammals and this may allow for higher concentrations of local anesthetic in the brain.³³ Respiratory arrest and subsequent successful resuscitation has been reported following procaine administration in a parakeet.³⁴

All birds showed rapid, shallow respiration (panting) at lower doses of lidocaine. Panting has been reported following lidocaine administration in cats.³⁵ Five birds showing convulsion or respiratory arrest recovered spontaneously without any treatment and one bird was successfully resuscitated. Rapid recovery is presumably related to rapid decline in blood levels due to dilution and redistribution of the local anesthetic. A recent pharmacokinetic study of lidocaine in chickens indicated that the rapid decrease in plasma concentration is due to redistribution of drug and large volume of distribution.³⁶ Chadwick (1985) reported a rapid decrease in lidocaine plasma level following termination of lidocaine infusion and during resuscitation in cats.¹⁷ Morishima et al. (1979) and Mihaly et al. (1978) reported that larger volume of distribution in newborns may result in higher dose requirement for toxic manifestation of lidocaine.³⁷⁻³⁸ It seems that rapid decrease in plasma concentration, together with larger volume of distribution and high rate of metabolism would explain the higher convulsive dose of lidocaine in chickens.

It has been reported that the rate of administration of local anesthetics may be important in determining central nervous system toxicity. The rapid infusion rates resulted in higher plasma concentrations, presumably because less time is available for redistribution and hepatic extraction.^{17,39}

We conclude that chickens can survive higher doses of lidocaine as compared to mammals. Clinical signs of systemic toxicity occurred at significantly higher blood concentration of lidocaine. Convulsion or respiratory arrest signals a potentially

life-threatening complication of local anesthetic overdose in chickens because the margin between recovery and death from convulsion and/ or respiratory arrest is narrow. Further studies are required to establish the safe dose of lidocaine in chickens and other avian species.

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چکیده

ارزیابی تجویز داخل رگی دوزهای بالای لیدوکائین در ماکیان (*Gallus domesticus*)

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هدف- تعیین دوز سمی و غلظت سرمی مرتبط با آن به دنبال بروز اثرات سمی داروی لیدوکائین در ماکیان

طرح مطالعه- مطالعه تجربی

حیوانات- هشت قطعه مرغ تخمگذار نژاد لوهمن با سن ۵۵ هفته و وزن $1/17 \pm 0/17$ کیلوگرم

روش کار- ابتدا یک دوز لیدوکائین ۰.۲٪ (۴ میلی‌گرم بر کیلوگرم) به صورت داخل رگی تجویز گردید و سپس به وسیله پمپ تزریق با دوز ۸ میلی‌گرم بر کیلوگرم بر دقیقه و به صورت انفوزیون وریدی با سرعت ثابت ادامه داده شد. به دنبال بروز تشنج یا ایست تنفسی واکنش مشاهده شده ثبت گردید و دوز سمی لیدوکائین محاسبه شد. همچنین برای تعیین غلظت سرمی لیدوکائین در زمان شروع تشنج یا ایست تنفسی، نمونه خونی اخذ گردید.

نتایج- دوز تام مسمومیت لیدوکائین و غلظت سرمی مرتبط با آن به ترتیب $28/96 \pm 6/21$ میلی‌گرم بر کیلوگرم و $38/5 \pm 10/4$ میکروگرم در میلی‌لیتر تعیین شد.

نتیجه گیری و کاربرد بالینی- بر پایه نتایج حاصل از این مطالعه در ماکیان نسبت به پستانداران، دوزهای بالاتری جهت بروز اثرات سمی داروی لیدوکائین مورد نیاز است.

کلید واژگان- لیدوکائین، انفوزیون، مسمومیت، ماکیان

