A study on reducing the absorption of lidocaine from the airway in cats[1]

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Abstract

Purpose: To determine if the combination of lidocaine with epinephrine or gamma globulin would decrease the rate or reduce the amount of local absorption of lidocaine through the airway.
Methods: Twenty adult male cats were randomly and evenly distributed into four groups: 1) Group LG: lidocaine administered with gamma globulin; 2) Group LS: lidocaine administered with physiological saline); 3) Group LE: lidocaine administered with epinephrine; 4) Group C: control group. Invasive blood pressure, heart rate, and concentration of lidocaine were recorded before and after administration.
Results: The peak of plasma concentrations appeared difference (Group LG: 1.39 ± 0.23 mg/L; Group LS: 1.47 ± 0.29 mg/L and Group LE: 0.99 ± 0.08 mg/L). Compared to Group C, there were significant differences in the average heart rate of Groups LG, LS, and LE ($P < 0.05$). The average systolic blood pressures were significantly different when each group was compared to Group C ($P < 0.05$). The biological half-life, AUC_{0-120}, peak time, and half-life of absorption among the three groups have not presented statistically significant differences ($P > 0.05$).
Conclusion: Administering lidocaine in combination with gamma globulin through airway causes significant decrease the rate and reduce the amount of local absorption of lidocaine in cats.
Key words: Bronchoscopy. Lidocaine. Epinephrine. Immunoglobulins. Trachea. Cats.

■ Introduction

Flexible bronchoscopy is a widely used clinical procedure performed by a variety of specialists[1]. However, complications, including isolated excessive coughing, excessive nausea reflex with coughing, oxygen desaturation to < 90%, and even death[2-5], may occur. A report by Suratt *et al.*[6] suggests that a major reason for mortality due to bronchoscopy may be related to pre-surgery anesthesia, and three cases of generalized seizures caused by lidocaine are presented. After being treated with lidocaine for local anesthesia, the toxicities and side-effects of lidocaine are mainly related with the peak plasma concentration, which can be toxic if it exceeds 5 mg/L and can cause a severe toxic reaction when the plasma concentration exceeds 10 mg/L. The maximum plasma concentrations of lidocaine were measured predominantly after 3 and 6 h and of lidocaine after 6 h. The patients' maximum plasma levels occurred 24 h after administration[7,8].

Lidocaine is metabolized by cytochrome P-4503A4(CYP3A4)tomonoethylglycinexylidide (MEGX), which is 80–90% more potent than lidocaine as an antiarrhythmic drug[9,10]. The protein binding percentages of both molecules are quite different. Lidocaine has a 60% to 70% protein binding affinity towards α1-acid glycoprotein compared to MEGX, which demonstrates a 15% affinity[11]. The risk of lidocaine toxicity is low because the peak lidocaine level is below the toxic threshold during an extensive bronchoscopic procedure or other surgeries[12,13]. The peak plasma concentration after the administration of lidocaine through the bronchoscope is mainly dependent on the total amount used and the individual differences of the patients, which contribute to the local excessive absorption, as well as happen when the functions of the organs like liver and heart are compromised, leading a impaired metabolism of lidocaine. In this way, any mechanism that can minimize the systemic absorption of such drug, or invalidate its free plasmatic portion, will become more safety to be administered.

Crystallography revealed a unique lidocaine binding site on human serum albumin. It showed that human serum proteins interact with local anesthetic agents. Therefore, we tested immunoglobulin in vivo for its ability to decrease lidocaine absorption via the airway[14]. The current work sought to determine if a mixture of lidocaine with epinephrine, gamma globulin, or physiological saline will result in different patterns of lidocaine absorption through the airway.

■ Methods

This study was reviewed and approved by the Committee of the Ethics on Animal Experiment in Department of Science Research, The Second Affiliated Hospital of Fujian Medical University.

A prospective, random, and comparative animal experiment method was used in this experiment. The healthy adult male cats (weights: 3-4 kg) were provided by the Animal Lab of Fujian Institution of Medical Science. The 20 adult male cats were evenly and randomly assigned into one of the four following groups (n=5): 1) Group LG: administered a mixture of lidocaine (5 ml: 0.1 g, Kangle Pharmaceutical CO., LTD, Zhejiang, China) and gamma globulin (ad mixture: 22 mg/kg of lidocaine with 1/2 volume gamma globulin; PH4, 2.5 g, Shanghai Xinxing Medicine Co., Ltd, Shanghai, China); 2) Group LS: administered a mixture of lidocaine with physiological saline (ad mixture: 22 mg/kg of lidocaine with 1/2 volume of physiological saline; 0.9%, Neptunus Futao Pharmaceuticals Co. Ltd., Fujian, China); 3) Group LE: administered a mixture of lidocaine with epinephrine (admixture of 22 mg/kg of lidocaine with 1:10000 epinephrine; 1 mg/

ml, Neptunus Futao Pharmaceuticals Co. Ltd., Fujian, China); or 4) Group C (control group) administered physiological saline at a volume that was 1.5 times greater than that of the 22 mg/kg of 2% lidocaine in order to counter the irritation caused by medicine instilled into the trachea.

Sedation and blood collection

Pentobarbital sodium (30 mg/kg; provided by the Animal Lab of Fujian Institution of Medical Science) was administered for anesthesia of the cats. An arterial cannula was inserted on one side of the carotid in order to continuously monitor the heart rate and invasive blood pressure. An intravenous *(IV)* catheter (BD Intima II, Closed IV Catheter System, Becton Dickinson Medical Devices Co. Ltd, Jiangsu, China) was inserted into the trachea, and the tip of the catheter was kept away from the thoracic entrance to ensure that the administration of medicine was into the trachea. We inserted an arterial cannula (BD Arterial Cannula, Becton Dickinson Critical Care Systems Pte Ltd, Singapore) on one side of the femoral artery. The cats were rested an hour after the surgery to eliminate the effects of the surgery on their heart rate and blood pressure. A 2-ml sample of arterial blood was drawn through the femoral artery catheter into an EDTA test tube for detection. A 2-ml sample of arterial blood was drawn from the catheter as a blank sample prior to the drug intervention, and the oscillogram recording of multipurpose polygraph was marked at the same time. Half of the total volume of the respective drug mixture was injected through the *IV* catheter that was inserted into the trachea. The timing of sample collection was measured from this point. A sample of the arterial blood was drawn at 30, 60, and 90 seconds. At 2 minutes, the remaining volume of the respective drug mixture was injected at a constant rate, followed immediately by 20 ml of air to fully discharge the remaining liquid. A sample of arterial blood was drawn at 2, 3, 5, 10, 15, 30, 60, 90, and 120 minutes.

Lidocaine plasma concentrations analysis

The lidocaine concentration of the solution was measured with high performance liquid chromatography (Shimadzu Corporation). The oscillogram recording of the multipurpose polygraph was marked as soon as each sample of blood was drawn in order to analyze the change of blood pressure (mmHg) and heart rate (beats per min) at different time points. The cats were euthanized and handled with innocent treatment after the experiment. Changes in heart rate and systolic and diastolic blood pressure were tested with the software that came with multipurpose polygraph. We selected the time 5 seconds before and after the drawing as the measuring period. The software would automatically measure and calculate the average value of the heart rate and systolic and diastolic blood pressures during this period.

Statistical analysis

Statistical analyses were performed with SPSS version 13.0 software (SPSS, Chicago, Illinois, USA) by analysis of variance (One way ANOVA) using Dunnett's or Tukey's test for multiple comparisons. The measured data were expressed as $\bar{x}$ ± S and rate was used to describe the counted data. The differences in the heart rate and systolic and diastolic blood pressure of each group at different time points were analyzed with the variance of repeated measurement design. The pharmacokinetic parameters were calculated using 3P97 computer software; the peak of plasma drug concentration, peak time, AUC, biological half-life, and the difference between the peaks of plasma drug concentration of two groups were analyzed with one way ANOVA. Statistical significance was set at $P < 0.05$.

■ Results

The weights of the cats used in each of the four groups were as follows: Group LG: 3.72 ± 0.26 Kg; Group LS: 3.78 ± 0.28 Kg; Group LE: 3.66 ± 0.23 Kg; and Group C: 3.56 ± 0.29 Kg. Based on the results of a one-factor analysis variance, the F-value among the four groups was 0.63 and the P-value was 0.61. No significant difference was observed.

Pharmacokinetics of the plasma concentrations in four groups

The plasma concentrations and drug-time curves of Groups LG, LS, and LE are shown in Figure 1A. The peak of plasma concentrations appeared at the following times: Group LG, 14.00 ± 5.48 minutes; Group LS, 8.40 ± 7.10 minutes; and Group LE, 7.40 ± 3.71 minutes. The peak concentration of Group LG was 1.39 ± 0.23 mg/L, the peak concentration of Group LS was 1.47 ± 0.29 mg/L, the peak concentration of Group LE was 0.99 ± 0.08 mg/L. The peak plasma concentration of Group LE decreased to 32.65% when compared to Group LS and 28.78% when compared to Group LG. The peak concentration of Group LE was significantly lower than that of Groups LG and LS (P = 0.016 and 0.012, respectively). There was no statistical difference between the peak concentration of Groups LG and LS (*P* = 0.716). The variance of peak concentration of Group LG was 8.93 times of that of Group LE, and the variance of Group LS was 10.30 times of that of Group LE. No statistical significance was found between Groups LG and LS (*P* = 0.865). Homogeneity tests on the variances of the dispersion of Groups LG, LS, and LE show that the dispersion of the latter group was significantly less than that of the former two groups (*P* = 0.006, *P* = 0.013, respectively).

The pharmacokinetic parameters of the three groups calculated by the 3P97 are presented in the Table 1. There was no statistical difference in the biological half-life, $AUC_{0\text{-}120}$, peak time, and half-life of absorption among the three groups (*P* > 0.05).

Table 1 - The pharmacokinetic parameters (Average±SD) of the three groups.

Group	Biological half-life t 1/2(K) min	$AUC_{0\text{-}120}$ (mg/L*min)	Value of peak time T(PEAK)min	Value of half-life of absorption t 1/2 (Ka) min
LG	41.50±12.59	68.30±23.18	9.44±6.75	2.60±2.71
LS	41.66±5.82	66.97±18.56	6.36±3.86	1.27±0.93
LE	52.92±14.95	57.82±14.96	5.43±2.64	0.94±0.51

Footnote: AUC: area under (the plasma concentration time) curve; SD: Standard Deviation

Effect on heart rate

The changes and the curved trends of the heart rates of the four groups are shown in Figure 1B. The statistical values are shown in Table 2. The heart rates of Group LG and Group LS decreased immediately after lidocaine was administered into the trachea. The heart rate of Group LG decreased 61.60 times/minute (from the baseline of 194.60 times/minute to the lowest value of 133.00 times/minute at 20 minutes), which was 31.65% of the baseline. In Group LS, it decreased 73 times/minute (from the baseline of 208.00 times/minute to the lowest value of 134.80 times/minute at 20 minutes), which was 35.10% of the baseline. Heart rates of the two groups gradually increased, but they did not return to baseline. No statistical difference was found in the changes between the two groups (*P* = 0.904).

The heart rate of Group LE remained stable during the first 20 minutes, then decreased 29.28 times/minutes (from the baseline 191.40 times/minute to its lowest value at 161.60 times/minute), which was 15.29% of the baseline. The decrease of this group was significantly moderate when compared to that of Groups LG and LS, and a statistical difference can be found (P = 0.000). The heart rate of Group C was stable. The largest decrease was 9.40 times/minute, accounting for 4.55% of the baseline. There was a slight increase in the heart rate 1 hour later. There were significant differences between the changes of Group C and those of the first three groups (P = 0.000). The trend in the degree of decreases in the heart rates among the four groups can be described as follows: Group LG and Group LS > Group LE > Group C.

Table 2 - The value of statistic of the changes trend of the heart rates of the four groups.

Group 1	Group 2	Repeated measures analysis of variance design (F)	Repeated measures analysis of variance design (P)
LG	LS	0.509	0.904
	LE	6.238	0.000
	C	9.712	0.000
LG	LE	8.635	0.000
	C	17.702	0.000
LE	C	13.197	0.000

Effect on blood pressure

The changes in the systolic blood pressure of the four groups are shown in Figure 1C. The systolic blood pressure of Groups LG and LS experienced the largest decrease. The systolic blood pressure of Group LG decreased 6.93 KPa (from a baseline of 29.04 KPa to the lowest value of 22.65 KPa at the 20 minutes), 22.00% of the baseline, and then slightly increase, but not return to baseline. The systolic blood pressure of Group LS decreased 7.52 KPa (from a baseline of 28.36 KPa to the lowest value of 20.84 KPa at 10 minutes), which was 26.52% of the baseline, and then slightly increased, but did not return to baseline. The systolic blood pressure of Group LE had a moderate decrease after 20 minutes and eventually decreased 3,41 KPa (from a baseline of 24.70 KPa to the lowest value of 21.29 KPa at 2 hours), which was 13.81% of the baseline. The systolic blood pressure of Group C decreased 3.31 KPa, which was 12.11% of the baseline, to its lowest value at 30 minutes. There was no statistical significance in the changes between Groups LG and LS (P = 0.633). The difference in changes between Groups LG and LE (P = 0.000), Groups LG and C (P = 0.000), Groups LS and LE (P = 0.000), Groups LG and C (P = 0.002), Groups LS and LE (P = 0.002), Groups LS and C (P = 0.002), and Groups LE and C (P = 0.001) were significantly different (Table 3). The trend in the degree of decrease in the systolic blood pressure among the four groups can be described as follows: Group LG and Group LS > Group LE > Group C (Figure 1C).

Table 3 - The statistical value of the changes trend of the systolic blood pressure of the four groups.

Group 1	Group 2	Repeated measures analysis of variance design (F)	Repeated measures analysis of variance design (P)
LG	LS	0.816	0.633
	LE	10.461	0.000
	C	4.143	0.000
LS	LE	6.421	0.000
	C	2.838	0.002
LE	C	3.177	0.001

The trend of the changes in the diastolic blood pressure of the four groups is shown in Figure 1D. The diastolic blood pressure of Group LG decreased 6.36 KPa (from a baseline of 20.62 KPa to the lowest value of 14.24 KPa at 20 minutes), which was 30.87% of the baseline, and then slightly increased, but did not return to baseline. In Group LS, it decreased 6.04 KPa (from a baseline of 19.86 KPa to the lowest value of 13.82 KPa at 10 minutes), which was 30.41% of the baseline, and then slightly increased, but did not return to baseline. In Group LE, it moderately decreased after 3 minutes and eventually decreased 3.54 KPa (from a baseline of 17.21 KPa to the lowest value of 13.67 KPa at 2 hours), which was 20.57% of the baseline. The diastolic blood pressure of Group C decreased 2.89 KPa, which was 14.85% of the baseline, to the lowest value at the 20 minutes. There was no significant difference in the change between Groups LG and LS ($P = 0.934$) and Groups LE and C ($P = 0.888$). However, there were significant differences in the change between Groups LG and LE ($P = 0.000$), LG and C ($P = 0.000$), LS and LE ($P = 0.000$), LS and C ($P = 0.0000$) (Table 4). The trend of the changes in the diastolic blood pressure among the four groups can be described as follows: Group LG and Group LS > Group LE > Group C (Figure 1D).

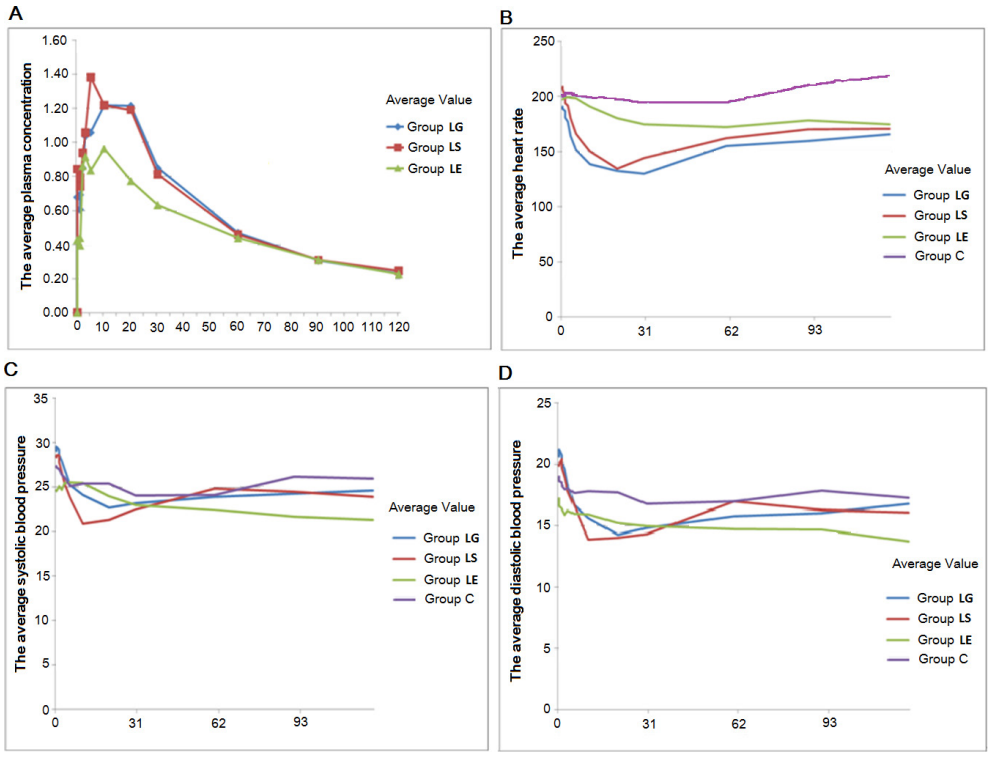

Figure 1 - The changes of the different indexes in each group at different points. **A**: The changes of the average plasma concentration of each group at each point; **B**: The changes of the average heart rate of each group at each point; **C**: The changes of the average systolic blood pressure of each group at each point; **D**: The changes of the average diastolic blood pressure of each group at each point.

Table 4 - The statistical value of the changes trend of the diastolic blood pressure of the four groups.

Group 1	Group 2	Repeated measures analysis of variance design (F)	Repeated measures analysis of variance design (P)
LG	LS	0.459	0.934
	LE	6.779	0.000
	C	5.227	0.000
LG	LE	3.754	0.000
	C	3.114	0.001
LE	C	0.533	0.888

■ Discussion

The combination of lidocaine with both epinephrine or gamma globulin is able to reduce its local rate of absorption as well as its total amount absorbed, when such solutions are administered in the airway. Considering that the clearance of a drug depends of organic blood flow, in such a way that the perfusion determines the rate of extraction to its metabolism, any condition affecting the cardiovascular system or the related organ, like the liver, for the lidocaine, may result in increased plasmatic levels and, as a consequence, lead to an adverse effect[15,16]. On the other hand, if a high dosage is absorbed from the site of administration, especially, when the local tissue has favorable property, like a bronchial mucosal tissue, a similar condition can be established. When the plasma concentration is within therapeutic range of 1 to 5 mg/L, it does not change the surface electrocardiogram (ECG). A severe toxic reaction includes reduced cardiac function, hypotension, reduced cardiac output, and, possibly, eventually death due to heart failure. The plasma concentration of the patients who were administered a single 2 mg/kg dose of lidocaine into the trachea was measured. The time to peak concentration was 0.75 minute and the peak plasma concentration reached 2.27 ± 0.92 mg/L[17,18], which suggests that lidocaine is well-absorbed through trachea. The drug concentration of Group LG was lower than that of Group LS after 10 minutes of treatment (Figure 1A). Taking into account the toxic effects, as far as plasmatic binding is concerned, some researches consider the gamma globulin as a second site of binding in serum for the lidocaine[19,20], since it can diminish the free fraction of such drug, and, as a consequence, lead to a lesser adverse effect. However, in the current experiment, the heart rate and blood pressure decreased similarly in Group LS and in Group LG, something that was statistically different of what happened with Groups LE and C, showing what could be considered a limitation of our study. On the other hand, when was considered the time to reach the peak plasma concentration, the observed result with the Group LG was different of what happened with the Groups LS and LE, suggesting the existence of a different mechanism, probably related to the gamma globulin, but that deserves further confirmation.

The administration of lidocaine through a bronchoscope is used often in clinical practice and its use continues to increase. The pharmacokinetic characteristics of gradual lidocaine application through the trachea are different from that of a single application[19]. The data from testing the bronchoscopic administration of drug showed that the plasma concentration of lidocaine depends on the total amount administered and the peak concentration values, which, in most patients, occurs between 5-30 minutes after drug delivery[20,21]. The peak plasma concentration of Group LS in this experiment was 8.40 ± 7.10 minutes, which was similar to the data from patients who received lidocaine administered

through the bronchoscope in clinical practice. It suggests that the animal model in this experiment can be used to simulate the changes in the arterial concentration of the patients in clinical practice who have had lidocaine administered through a bronchoscope.

The toxic and side-effects of lidocaine are mainly determined by the peak plasma concentration[17]. Slowing down or reducing the rate of absorption of lidocaine is an important way to reduce the peak plasma concentration and the toxic and side-effects of administering lidocaine via the airway. In this study, we mainly focused on the effects of two methods of administration on the absorption of lidocaine through the airway. First was used an agent with a mixed effect of α and β receptor stimulation that causes a bronchial mucosal contraction and is a vascular agent (adrenaline). It performs by 3 mechanisms. (1) It affects vasomotion and blood pressure and mainly has an impact on small arteries and the precapillary sphincter. The β2 receptor of blood vessels is more sensitive to adrenaline at low concentrations and can cause skeletal muscles to contract and blood vessels and coronary blood vessels to expand, which leads to a temporary decrease in blood pressure. The α-adrenergic receptor, which is stimulated by middle-range doses, can make the blood vessels of the skin and internal organs contract, which increases the systolic blood pressure. The effect of the β2 receptor balances the effect of contraction of the blood vessels in the skin and internal organs, which causes the diastolic blood pressure to either remain unchanged or decrease and increases the pulse pressure. A high concentration of adrenaline can make the blood vessels of the skin and internal organs contract strongly, which exaggerates the dilatation of the skeletal muscle and coronary vasculature and leads to the increase of the diastolic blood pressure. (2) It excites the heart by increasing cardiac contractility, accelerating the signal transmission, increasing the heart rate, and increasing cardiac output. (3) It also expands the bronchus and promotes metabolism. Based on the above-mentioned pharmacological properties of adrenaline, it is possible that it causes a decrease in the absorption of lidocaine either through the contraction of the bronchial mucous membrane, and/or it balances out part of the side-effects of lidocaine when epinephrine and lidocaine are absorbed into blood at the same time. Some studies have shown that the amount of epinephrine in dental cartridges is so low that use of one to three cartridges of lidocaine with epinephrine is safe and has no considerable effect on cardiac parameters, including blood pressure and heart rate[22]. Second is the use of a mixed acidic colloid protein (gamma globulin). Lidocaine is alkaline, and it can be combined with the α1-acid glycoprotein in the blood when in the blood circulation[23]. While the gamma globulin is an acid colloid (pH = 4), it may be combined with lidocaine and may slow down the speed of absorption of lidocaine.

We found that individual differences exist in the absorption of lidocaine in Groups LG and LS after the delivery of lidocaine to the trachea. Although the same amount of lidocaine per kilogram of body weight was used, the variability of peak plasma concentration was widely distributed. This result may explain why the plasma drug concentrations of most patients are under 5 mg/L, but the plasma drug concentrations of some patients can be significantly higher, while a small number of patients can even have severe systemic side effects, such as convulsions and cardiac arrest, when they are administered the same amount of lidocaine through a bronchoscope in clinical practice. The variance in the peak plasma concentration of Group LE is significantly less than that of Groups LG and LS, which suggests that epinephrine may prevent the local excessive absorption of lidocaine by

contracting the blood vessels of the bronchial mucous membrane, causing lidocaine to be evenly absorbed through the airway, thereby enhancing the safety of the bronchoscopic administration of lidocaine.

The peak plasma concentration of lidocaine mixed with adrenaline was significantly lower than that of lidocaine mixed with normal saline or gamma globulin. It decreases by 28.78% and 32.65% compared to the latter two, respectively. This suggests that the peak plasma concentration can be significantly decreased by mixing lidocaine with adrenaline. It interferes with the absorption of lidocaine through airway by contracting the blood vessels of bronchial mucous membrane, which is valuable to improve the security of the application of through bronchoscope[24]. In contrast, the peak plasma concentration cannot be decreased by mixing lidocaine with gamma globulin. Whether other acid colloids can influence the pharmacokinetics of the absorption of lidocaine from the airway needs further exploration.

Here, changes in heart rate, systolic blood pressure, and diastolic blood pressure were comparatively synchronized after administering lidocaine into the airway. The heart rate, systolic blood pressure, and diastolic blood pressure in group LS apparently decreased after lidocaine was administered (heart rate, systolic blood pressure and diastolic blood pressure decreased by 35.10%, 26.51%, 30.41%, respectively). The heart rate, systolic blood pressure, and diastolic blood pressure of the group that was administered the mix with gamma globulin experienced a similar change, and no effect on the observed parameters was found. In the group where epinephrine was used in the mix, the heart rate and blood pressure decreased, but the degree of change was significantly more moderate when compared to that of the groups where normal saline and gamma globulin were used. The pharmacokinetic results show that mixing with adrenaline decreases the peak plasma concentration, while physiologically, the cardiovascular side-effects of lidocaine are decreased.

We found that the mixed-adrenaline abates the cardiovascular side-effects of lidocaine by decreasing its peak plasma concentration, stimulating the heart and increasing the heart rate through excitation of the β2 receptors after absorption into the blood via the airway simultaneously or sequentially with lidocaine, increasing the systolic and diastolic blood pressure through excitation of the α receptors, and then countering the decrease in heart rate and blood pressure caused by lidocaine. When lidocaine was mixed with gamma globulin, the peak plasma concentration did not decrease, pharmacokinetics was not impacted, and there was no abatement of the lidocaine's cardiovascular effects (heart rate and systolic and diastolic blood pressure). The possible reasons are as follows: (1) lidocaine cannot bind gamma globulin under the different *in vivo* and *in vitro* conditions, or they are able to bind, but the affinity is weak; therefore, it does not impede the absorption of lidocaine; (2) lidocaine simultaneously possesses fat-soluble and water-soluble properties as well as strong penetrability; therefore, the colloids cannot interfere with the absorption of lidocaine.

This experiment suggests that the mixture with adrenaline at 1:10000 can decrease the plasma concentrations of lidocaine to reduce its cardiovascular side effects. Adrenaline itself can be absorbed through the airway; therefore, the inappropriate concentration of adrenaline itself can lead to other side effects. It is necessary to determine the reasonable proportion of adrenaline and lidocaine to increase the safety. Further research for other colloids that can affect the pharmacokinetics of lidocaine and for determination of their safety

profiles in the respiratory tissues is needed. The limitation is that the small size and the molecular mechanism are unclear.

■ Conclusion

Gamma globulin and epinephrine play important roles in the reduction of the local absorption of lidocaine via the airway, since it has been shown in cats that the administration of 22 mg/kg lidocaine into the trachea can significantly decrease the rate and reduce the amount of local absorption of lidocaine in cats.

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