Laboratory Investigations

Modification of intravenous lidocaine-induced convulsions by epinephrine in rats

Masataka Yokoyama MD,* Hiroshi Goto MD,*
Wasa Ueda MD,† Masahisa Hirakawa MD,‡
Kasumi Arakawa MD*

We studied intravenous lidocaine-induced convulsions in rats to determine whether added epinephrine influences the provocation of lidocaine toxicity. Wistar rats (200–250 g) were divided into three groups of ten, depending on the concentration of epinephrine added to lidocaine. Group 1: plain 1.5% lidocaine; Group 2: 1.5% lidocaine with 1:200,000 epinephrine; Group 3: 1.5% lidocaine with 1:100,000 epinephrine. After surgical preparation and recovery from anaesthesia, all rats received a continuous iv infusion of lidocaine ($15 \text{ mg} \cdot \text{ml}^{-1}$) at a rate of $4.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until generalized convulsions occurred. The epinephrine-treated animals developed acute hypertension after one minute of lidocaine infusion (105 ± 2 to $141 \pm 2 \text{ mmHg}$ in Group 2 and 103 ± 2 to $151 \pm 2 \text{ mmHg}$ in Group 3). The PaO_2 values in the epinephrine groups at the onset of convulsions were decreased significantly (88.3 ± 1.0 to $84.0 \pm 1.5 \text{ mmHg}$ in Group 2 $P < 0.05$ and 86.9 ± 1.2 to 78.1

Key words

ANAESTHETICS, LOCAL: lidocaine;

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From the *Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas 66160-7415, USA; †Department of Anesthesiology and Resuscitology, Kochi Medical School, Nankoku City, Kochi 783, Japan; and the ‡Department of Anesthesiology and Resuscitology, Okayama University Medical School, Okayama City, Okayama 700, Japan.

Address correspondence to: Dr. Hiroshi Goto, Department of Anesthesiology, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160-7415, USA.

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$\pm 2.4 \text{ mmHg}$ in Group 3 $P < 0.01$). However, these values were still within physiological ranges. Serum potassium concentrations in all groups were decreased $P < 0.05$, (4.24 ± 0.09 to $3.52 \pm 0.12 \text{ mEq} \cdot \text{L}^{-1}$ in Group 1, 4.02 ± 0.09 to $3.63 \pm 0.17 \text{ mEq} \cdot \text{L}^{-1}$ in Group 2, and 4.15 ± 0.10 to $3.69 \pm 0.17 \text{ mEq} \cdot \text{L}^{-1}$ in Group 3). Blood sugar concentrations in all groups were increased at the onset of convulsions, and the levels in the epinephrine groups were higher than in Group 1 $P < 0.01$ (119 ± 4 to $149 \pm 7 \text{ mg} \cdot \text{dl}^{-1}$ in Group 1; 120 ± 4 to $195 \pm 10 \text{ mg} \cdot \text{dl}^{-1}$ in Group 2, and 127 ± 3 to $190 \pm 6 \text{ mg} \cdot \text{dl}^{-1}$ in Group 3). There were differences in the cumulative convulsant doses of lidocaine among the groups, as follows: Group 1 = $41.9 \pm 1.3 >$ Group 2 = $30.0 \pm 0.7 >$ Group 3 = $24.2 \pm 0.9 \text{ mg} \cdot \text{kg}^{-1}$; $P < 0.01$. At the onset of convulsions, not only the plasma lidocaine concentrations (Group 1 = $10.7 \pm 0.3 >$ Group 2 = 8.3 ± 0.2 ($P < 0.01$) $>$ Group 3 = $7.5 \pm 0.2 \mu\text{g} \cdot \text{ml}^{-1}$ ($P < 0.01$ vs Group 1, $P < 0.05$ vs Group 2), but also the brain lidocaine concentrations which were extracted from the whole brain homogenates: Group 1 = $48.7 \pm 1.9 >$ Group 2 = 38.2 ± 1.1 ($P < 0.01$) $>$ Group 3 = $33.0 \pm 1.3 \mu\text{g} \cdot \text{g}^{-1}$ ($P < 0.01$ vs Group 1, $P < 0.05$ vs Group 2) showed differences. The brain/plasma lidocaine concentration ratios were, however, similar in the three groups (Group 1 = 4.5 ± 0.1 ; Group 2 = 4.6 ± 0.1 ; Group 3 = 4.4 ± 0.2). Our data show that added epinephrine decreases the threshold of lidocaine-induced convulsions dose-dependently; however, the added epinephrine does not cause a greater proportion of the infused lidocaine to enter the CNS.

Nous avons provoqué des convulsions par l'injection intraveineuse de lidocaine chez le rat pour de déterminer si l'addition d'épinephrine influençait l'apparition de la toxicité. Des rats de race Wistar (200–250 g) ont été répartis en trois groupes de dix d'après la quantité d'épinephrine ajoutée à la lidocaine. Groupe 1: lidocaine simple 1,5%; groupe 2: lidocaine 1,5% adrénalinée à 1:200,000; groupe 3: lidocaine 1,5% adrénalinée à 1:100,000. Après préparation chirurgicale et récupération de

l'anesthésie, tous les rats reçoivent une perfusion continue de lidocaïne (15 mg · ml⁻¹) à la vitesse de 4,0 mg · kg⁻¹ · min⁻¹ jusqu'à l'apparition de convulsions généralisées. Chez les animaux traités à l'épinéphrine, une hypertension aiguë apparaît après une minute de perfusion de lidocaïne (de 105 ± 2 à 141 ± 2 mmHg dans le groupe 2, et de 103 ± 2 à 151 ± 2 mmHg dans le groupe 3). Dès le début des convulsions, les valeurs de PaO₂ des groupes épinéphrine diminuent (88,3 ± 1,0 à 84 ± 1,5 mmHg dans le groupe 2, $P < 0,05$) et de 86,9 ± 1,2 à 78,1 ± 2,4 mmHg dans le groupe 3, $P < 0,05$) tout en demeurant toujours en l'intérieur des limites physiologiques. La kaliémie diminue ($P < 0,05$) dans tous les groupes (de 4,24 ± 0,09 à 3,52 ± 0,12 mEq · L⁻¹ dans le groupe 1, 4,02 ± 0,09 à 3,63 ± 0,17 mEq · L⁻¹ dans le groupe 2, et 4,15 ± 0,10 à 3,69 ± 0,17 mEq · L⁻¹ dans le groupe 3). La glycémie augmente dans tous les groupes au début des convulsions mais plus que dans le groupe 1, $P < 0,01$ (de 119 ± 4 à 149 ± 7 mg · dl⁻¹ dans le groupe 1, de 120 ± 4 à 195 ± 10 mg · dl⁻¹ dans le groupe 2, et de 127 ± 3 à 190 ± 6 mg · dl⁻¹ dans le groupe 3). On trouve des différences entre les doses convulsivantes cumulatives: groupe 1 = 41,9 ± 1,3 > groupe 2 = 30,0 ± 0,7 > groupe 3 = 24,2 ± 0,9 mg · kg⁻¹, $P < 0,01$. Au début des convulsions, non seulement les concentrations plasmatiques de lidocaïne sont-elles plus élevées (groupe 1 = 10,7 ± 0,3 > groupe 2 = 8,3 ± 0,2 ($P < 0,01$) groupe 3 = 7,5 ± 0,2 µg · ml⁻¹ ($P < 0,01$ vs groupe 1, $P < 0,05$ vs groupe 2), mais les concentrations cérébrales de lidocaïne extraites des homogénats de cerveaux complets présentent aussi des différences: groups 1 = 48,7 ± 1,9 > group 2 = 38,2 ± 1,1 ($P < 0,01$) > groupe 3 = 33,0 ± 1,3 µg · g⁻¹ ($P < 0,01$ vs groupe 1, $P < 0,05$ vs groupe 2). Le rapport cerveau plasma pour la concentration de lidocaïne demeure toutefois identique pour les trois groupes (groupe 1 = 4,5 ± 0,1; groupe 2 = 4,6 ± 0,1; groupe 3 = 4,4 ± 0,2). Ces données montrent que l'addition d'épinéphrine produit une diminution dépendante de la dose liminale des convulsions provoquées par la lidocaïne; cependant, l'addition de lidocaïne n'augmente pas la proportion de pénétration cérébrale de la lidocaïne.

The addition of epinephrine to lidocaine has several beneficial effects. Epinephrine improves the quality of major conduction block¹ in addition to increasing the duration of the block. Epinephrine decreases the amount of surgical blood loss and serves as an indicator of accidental intravascular injection.² The addition of epinephrine is especially beneficial from the viewpoint of lidocaine toxicity, since the vasoconstrictive action of epinephrine decreases peak plasma concentrations of lidocaine after local infiltration or nerve blocks. Therefore, lidocaine solutions containing epinephrine are widely used clinically.

Yagiela³ and Torbiner *et al.*⁴ reported that an intravenous bolus injection of lidocaine with 1:100,000 epi-

nephrine lowered the convulsant as well as the lethal doses of lidocaine in rats. However, they did not measure plasma and brain lidocaine concentrations or haemodynamic and metabolic changes. To our knowledge, the effects of different concentrations of epinephrine on lidocaine-induced convulsions have not been studied. We employed an awake rat model of lidocaine-induced convulsions to determine if different doses of added epinephrine might influence the provocation of lidocaine-induced convulsions, and to elucidate the possible mechanisms by which epinephrine lowers convulsant doses of lidocaine.

Methods

This study was approved by the institutional animal care and use committee. The animals were fasted for six hours (water was supplied *ad libitum*), and the experiments were performed between 1 and 5 pm.

Thirty male Wistar rats weighing 200–250 g (7–8 wk old) were anaesthetized with halothane in oxygen during surgical preparation. One of the femoral arteries was cannulated with a polyethylene catheter to monitor mean arterial blood pressure (MAP) and heart rate (HR), and for blood sampling. The femoral vein was also cannulated for infusion of lidocaine with and without epinephrine. The proximal ends of these catheters were tunneled subcutaneously to the posterior cervical region so that the animals could move freely. Before emergence from anaesthesia, the animals were placed in a plastic container to recover for two hours before the experiment.

The animals were divided into three groups of ten, depending on the concentration of added epinephrine. Animals in Group 1 received plain 1.5% lidocaine; Group 2 received 1.5% lidocaine with 1:200,000 epinephrine, and Group 3 received 1.5% lidocaine with 1:100,000 epinephrine (lidocaine: lidocaine hydrochloride, Lyphomed Inc., Rosemont, IL). All groups received a continuous *iv* infusion of lidocaine (15 mg · ml⁻¹) at a rate of 4.0 mg · kg⁻¹ · min⁻¹ (0.053–0.067 ml · min⁻¹) by infusion pump until generalized convulsions occurred. The calculated infusion rates of added epinephrine were as follows: Group 2, 1.33 µg · kg⁻¹ · min⁻¹ and Group 3, 2.66 µg · kg⁻¹ · min⁻¹. Total lidocaine doses from the beginning of infusion to the onset of convulsions were calculated for each animal as: infusion rate × infusion time.

Arterial blood pressure and HR were monitored and recorded continuously, and the animals were observed continuously for generalized convulsions.

Arterial blood, 0.5 ml, was drawn just before the beginning of the lidocaine infusion, and 1.5 ml at the onset of convulsions to determine blood gas tensions, pH, serum sodium, serum potassium, blood sugar and plasma lidocaine concentrations (serum sodium and potassium, and blood sugar were measured in six animals of each

TABLE I Circulatory change

	Group	Baseline	1 min	5 min	IBC
MAP (mmHg)	1	102 ± 2	103 ± 2	104 ± 2	102 ± 2
	2	105 ± 2	141 ± 2*§	140 ± 2*§	140 ± 2*§
	3	103 ± 2	151 ± 2*§¶	151 ± 2*§¶	152 ± 2*§¶
HR (b.p.m.)	1	423 ± 7	389 ± 8*	359 ± 9*¶	329 ± 11*†**
	2	421 ± 7	364 ± 7*††	378 ± 5*	418 ± 7§††
	3	425 ± 7	354 ± 10*§	385 ± 8*††	413 ± 9§†**

Values are means ± SEM; *n* = 10.

MAP: mean arterial blood pressure; HR: heart rate.

IBC: immediately before convulsions.

Group 1: plain lidocaine; Group 2: lidocaine with 1:200,000 epinephrine; Group 3: lidocaine with 1:100,000 epinephrine.

P* < 0.01 vs baseline; †*P* < 0.01 vs 1 min; ‡*P* < 0.01 vs 5 min; §*P* < 0.01 vs Group 1; ¶*P* < 0.01 vs Group 2; ||*P* < 0.05 vs 1 min; *P* < 0.05 vs 5 min; ††*P* < 0.05 vs Group 1.

group). The brains were also rapidly removed and weighed at the onset of convulsions. Homogenates were made from the whole brain, and brain lidocaine was extracted and analyzed. For determination of serum electrolytes concentration, blood sugar and plasma lidocaine concentrations, blood samples were centrifuged and the serum and plasma were frozen at -80°C until analyzed. Serum electrolyte concentrations were measured with a CIBA-CORNING blood gas analyzer (Model 288 Medifield, MA), and blood sugar was determined by the glucose-oxidase method. Lidocaine concentrations were determined by high-performance liquid chromatography (HPLC) with a UV spectrometer, using a LC-6A pump and SPD-6A detector (Shimadzu, Kyoto, Japan). We employed the method of analysis introduced by Satoh.⁵ The analytical conditions were as follows: the column, Shim-Pack (ODS) 4.6 × 250 mm (Shimadzu); the mobile phase, 0.05 M KH_2PO_4 , 0.05 M K_2HPO_4 /acetonitrile pH 4.0 (88:12 vol/vol).

Obtained data were expressed as means ± SEM. Statistically significant differences were determined by one-way or two-way analysis of variance followed by Duncan's method, and *P* < 0.05 was considered significant.

Results

Baseline MAP and HR were similar for the three groups (Table I). The MAP in Group 1 did not change until the onset of convulsions. In the epinephrine groups (Groups 2 and 3), however, MAP increased, and the values in Group 3 were higher than in Group 2 after lidocaine infusion until the onset of convulsions. The HRs decreased after one minute of infusion in all groups. The reduction of HR in the epinephrine groups was greater than in Group 1. Thereafter, the HR in Group 1 decreased continuously until the onset of convulsions. On the con-

trary, the epinephrine groups showed gradual recovery in HR toward the baseline values, before the onset of convulsions.

Baseline blood gas, electrolyte and blood sugar data in the three groups were similar (Tables II, III). At the onset of convulsions, PaO_2 values in the epinephrine groups were decreased compared with baseline values, and PaO_2 values in Group 3 were lower than in the other two groups. The concentrations of serum potassium in all groups were decreased at the onset of convulsions. Blood sugar values in all groups were increased at the onset of convulsions, and the sugar levels in the epinephrine groups were greater than in Group 1.

There were differences among all groups in the cumulative convulsant doses of infused lidocaine; i.e., Group 1 > Group 2 > Group 3 (*P* < 0.01) (Table IV). The plasma lidocaine concentrations at the onset of convulsions indicated that Group 1 > Group 2 (*P* < 0.01) > Group 3 (*P* < 0.01 vs Group 1 and *P* < 0.05 vs Group 2) (Table IV). The brain lidocaine concentrations at the onset of convulsions also showed Group 1 > Group 2 (*P* < 0.01) > Group 3 (*P* < 0.01 vs Group 1 and *P* < 0.05 vs Group 2) (Table IV). The brain/plasma concentration ratios were similar for the three groups (Table IV).

Discussion

Yagiela³ and Torbiner *et al.*⁴ reported that the addition of epinephrine (1:100,000) to lidocaine decreased the lethal as well as the convulsant bolus doses of lidocaine in awake rats. Bernards *et al.*⁶ reported that the addition of epinephrine (1:200,000) to bupivacaine decreased the cumulative convulsant dose when bupivacaine was infused at a rate of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in pigs. However,

TABLE II Analyses of blood gases

	Group	Baseline	Convulsions
pHa	1	7.44 ± 0.01	7.43 ± 0.01
	2	7.44 ± 0.01	7.43 ± 0.01
	3	7.43 ± 0.01	7.41 ± 0.01
PaO ₂ (mmHg)	1	88.1 ± 0.9	88.1 ± 0.9
	2	88.3 ± 1.0	84.0 ± 1.5*
	3	86.9 ± 1.2	78.1 ± 2.4†‡§
PaCO ₂ (mmHg)	1	37.0 ± 0.9	36.4 ± 0.5
	2	36.5 ± 1.0	37.0 ± 1.3
	3	37.6 ± 0.7	40.0 ± 1.4
HCO ₃ (mEq · L ⁻¹)	1	25.2 ± 0.4	24.3 ± 0.3
	2	24.4 ± 0.6	24.6 ± 0.6
	3	25.2 ± 0.5	25.1 ± 0.7

Values are means ± SEM. *n* = 10.

Group 1: plain lidocaine.

Group 2: lidocaine with 1:200,000 epinephrine.

Group 3: lidocaine with 1:100,000 epinephrine.

†*P* < 0.01 vs baseline; ‡*P* < 0.01 vs Group 1; §*P* < 0.05 vs Group 2;

**P* < 0.05 vs baseline.

the mechanisms by which epinephrine lowers the convulsant doses have not been clearly elucidated. Yagiela and Torbiner's bolus injection models are more applicable to the clinical situation than our continuous infusion model, but it is impossible to investigate the haemodynamic and metabolic changes in the bolus injection study.

Our results showed that epinephrine decreased the cumulative convulsant doses of lidocaine, and the higher the concentration of added epinephrine, the lower the cumulative convulsant dose of infused lidocaine. Yagiela *et al.*^{3,4} speculated that epinephrine altered the distribution of blood by affecting some vessels more than others, and probably caused a greater proportion of the infused lidocaine to enter the CNS. Bernards *et al.*⁶ also speculated that the CNS was exposed to a higher plasma concentration of bupivacaine in the presence of epinephrine. However, our results elucidated that not only the plasma lidocaine concentrations but also the brain lidocaine concentrations at the onset of convulsions were decreased by epinephrine, and the brain/plasma concentration ratios were similar for the three groups. This means that the added epinephrine did not cause a greater proportion of the infused lidocaine to enter the CNS.

Several investigators⁷⁻⁹ have reported that acute hypertension can cause leakage of the blood-brain barrier in animals, and Häggendal and Johansson¹⁰ reported that leakage of the blood-brain barrier depends on the rate at which the blood pressure is raised. However, our results showed that the higher the increase in MAP, the lower the brain lidocaine concentrations (Figure). Therefore,

TABLE III Analyses of electrolytes and blood sugar

	Group	Baseline	Convulsions
Na ⁺ (mEq · L ⁻¹)	1	141.7 ± 0.4	142.5 ± 0.8
	2	140.7 ± 0.6	138.7 ± 1.2
	3	140.2 ± 0.9	139.0 ± 1.6
K ⁺ (mEq · L ⁻¹)	1	4.24 ± 0.9	3.52 ± 0.12*
	2	4.02 ± 0.9	3.63 ± 0.17*
	3	4.15 ± 0.10	3.69 ± 0.17*
Blood sugar (mg · dl ⁻¹)	1	119 ± 4	149 ± 7†
	2	120 ± 4	195 ± 10†‡
	3	127 ± 3	190 ± 6†‡

Values are means ± SEM. *n* = 6.

Group 1: plain lidocaine.

Group 2: lidocaine with 1:200,000 epinephrine.

Group 3: lidocaine with 1:100,000 epinephrine.

**P* < 0.05 vs baseline; †*P* < 0.01 vs baseline; ‡*P* < 0.01 vs Group 1.

leakage of the blood-brain barrier was unlikely in our experiment model.

Although the PaO₂ levels in the epinephrine groups were decreased at the onset of convulsions, these values were still within physiological ranges. It is difficult to consider this small reduction of PaO₂ as the reason for decreasing the threshold of convulsions in the epinephrine groups. However, we did not measure cardiac output or cerebral blood flow. If cerebral blood flow in the epinephrine groups were decreased markedly, the reduction of PaO₂ could have caused severe hypoxia in the brain and reduced the threshold for convulsions.

The concentrations of serum potassium in all groups were decreased at the onset of convulsions. However, there were no differences among the three groups, and these values were maintained within physiological ranges. Avery *et al.*¹¹ reported that a change in serum potassium (2.7–5.4 mEq · L⁻¹) did not alter the cumulative convulsant doses of lidocaine in dogs. Therefore, it is unlikely that the reduction of serum potassium in the epinephrine groups affected the threshold of lidocaine-induced convulsions. Although an increase in plasma epinephrine in the epinephrine groups may have decreased serum potassium,¹² this is unlikely, since the same degree of reduction of serum potassium also was observed in the control group; but the reason for this reduction is not clear.

Elevation in blood sugar at the time of convulsions in animals has been reported,^{13,14} and epinephrine itself elevates blood sugar concentration. Our results also showed elevation in blood sugar in all groups at the onset of convulsions, and the values in the epinephrine groups were greater than in the control group. The elevation in blood sugar would have been an unlikely reason for low-

TABLE IV Cumulative convulsant doses and plasma and brain concentrations of lidocaine

Group	Dose (mg · kg ⁻¹)	Plasma conc. (μg · mL ⁻¹)	Brain conc. (μg · g ⁻¹)	Brain/plasma conc. ratio
1	41.9 ± 1.3	10.7 ± 0.3	48.7 ± 1.9	4.5 ± 0.1
2	30.0 ± 0.7*	8.3 ± 0.2*	38.2 ± 1.1*	4.6 ± 0.1
3	24.2 ± 0.9*†	7.5 ± 0.2**	33.0 ± 1.3*‡	4.4 ± 0.2

Values are means ± SEM; *n* = 10.

Group 1: plain lidocaine; Group 2: lidocaine with 1:200,000 epinephrine.

Group 3: lidocaine with 1:100,000 epinephrine.

**P* < 0.01 vs Group 1; †*P* < 0.01 vs Group 2; ‡*P* < 0.05 vs Group 2.

FIGURE Relationship between brain lidocaine concentrations at the onset of convulsions and MAP. MAP represents the rise of mean arterial blood pressure for the first one minute of infusion.

ering the threshold of convulsions, because there were no differences between the sugar level in Groups 2 and 3, although there were differences in plasma and brain lidocaine concentrations.

We could not elucidate the mechanism by which epinephrine lowered the threshold of lidocaine-induced convulsions. Nevertheless, several possibilities may be considered. First, cerebral blood flow and cerebral oxygenation might have decreased. Second, the lidocaine concentrations of a specific area in the brain which is considered to affect lidocaine-induced convulsions might have increased in the epinephrine groups. Third, epinephrine itself might have affected lidocaine toxicity. Although our preliminary study showed that continuous infusion of 1:100,000 epinephrine in normal saline solution at the same rate as used in this study did not cause convulsions, epinephrine may have changed the threshold of lidocaine-induced convulsions.

In conclusion, our data showed that added epinephrine reduced the threshold of lidocaine-induced convulsions in a dose-dependent fashion, and the ratios of brain/plasma lidocaine concentrations were not altered by added epinephrine. The mechanisms by which epinephrine lowers the threshold of lidocaine-induced convulsions should be studied further.

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