Laboratory Report

Lidocaine prolongs the safe duration of circulatory arrest during deep hypothermia in dogs

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Purpose: To test the hypothesis that lidocaine prolongs the safe period of circulatory arrest during deep hypothermia.

Methods: Sixteen dogs were subjected to cooling, first surface cooling to 30°C and then core cooling to 20°C rectal temperature). The circulation was then stopped for 90 min. In the lidocaine group, 4 mg·kg⁻¹ lidocaine was injected into the oxygenator two minutes before circulatory arrest and 2 mg·kg⁻¹ at the beginning of reperfusion and rewarming. The control group received equivalent volumes of normal saline. Post-operatively, using a neurological deficit scoring system (maximum deficit score - 100; minimum - zero indicating that no scored deficit could be detected). Neurological function was evaluated hourly for six hours and then daily for one week. the pharmacokinetic parameters were calculated using one compartment model.

Results: On the seventh day, the neurological deficit score and overall performance were better in the lidocaine (0.83 ± 2.04) than in the control group (8.33 ± 4.08 $P < 0.05$). During the experiment, the base excess values were also better in the lidocaine than in the control group (at 30 min reperfusion: -4.24 ± 1.30 vs -8.20 ± 2.82 $P < 0.01$, at 60 min reperfusion was -3.34 ± 1.87 vs -7.52 ± 2.40 ($P < 0.01$). On the eighth day the extent of pathological changes were milder in the lidocaine group than that in the control group. The elimination half life of lidocaine was 40.44 ± 7.99 during hypothermia and 2.01 ± 4.56 during rewarming.

Conclusions: In dogs lidocaine prolongs the safe duration of circulatory arrest during hypothermia.

Objectif : Vérifier l'hypothèse qui veut que la lidocaïne prolonge la période sans risque d'arrêt circulatoire sous hypothermie profonde.

Méthode : Seize chiens ont été soumis à un refroidissement, externe d'abord jusqu'à 30 °C, puis interne jusqu'à une température rectale de 20 °C. La circulation a été arrêtée ensuite pendant 90 min. Dans le groupe ayant reçu de la lidocaïne, 4 mg×kg⁻¹ de lidocaïne ont été injectés dans l'oxygénéateur deux minutes avant l'arrêt de la circulation et 2 mg×kg⁻¹ au début de la reperfusion et du réchauffement. Le groupe témoin a reçu des quantités équivalentes de solution salée. Après l'intervention, au moyen d'un système de cotation du déficit neurologique (déficit maximal - 100; minimal - zéro, indiquant qu'aucune baisse n'a été détectée dans cette échelle de cotation), la fonction neurologique a été évaluée à toutes les heures pendant six heures et, par la suite, à chaque jour pendant une semaine. Les paramètres pharmacocinétiques ont été calculés avec l'emploi d'un modèle mono-compartmental.

Résultats : Le septième jour, la cotation du déficit neurologique et le rendement global ont été meilleurs dans le groupe avec la lidocaïne (0,83 ± 2,04) que dans le groupe témoin (8,33 ± 4,08 $P < 0,05$). Pendant l'expérience, les valeurs de l'excès basique ont aussi été meilleures dans le groupe avec lidocaïne que dans le groupe témoin (30 min. après le début de la reperfusion: -4,24 ± 1,30 vs -8,20 ± 2,82 $P < 0,01$; à 60 min. -3,34 ± 1,87 vs -7,52 ± 2,40 $P < 0,01$). Le huitième jour, l'étendue des changements pathologiques a été moins importante toujours dans le groupe avec lidocaïne. La demi-vie d'élimination de la lidocaïne était de 40,44 ± 7,99 pendant l'hypothermie et de 2,01 ± 4,56 pendant le réchauffement.

Conclusion : Chez les chiens soumis à une hypothermie, la lidocaïne prolonge la période sans risque d'arrêt circulatoire.

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LIDOCAINE has membrane stabilizing properties and reduces cerebral metabolism.^{1,2} These affects are thought to contribute to lidocaine's potential as a cerebral protective agent. Studies in our laboratory as well as by others have demonstrated that lidocaine can delay the onset of ischaemic potassium efflux as well as showing a beneficial affect on other indicators of ischaemic and reperfusion brain injury.³⁻⁵

In general, lidocaine pre-treatment results in a better outcome than post-ischaemic treatment.⁴ Also, lidocaine and hypothermia have additive effects.⁶ These studies suggested that lidocaine may prolong the safe duration of hypothermic circulatory arrest. The aims of the present study were to test this hypothesis and to document the pharmacokinetic behaviour of lidocaine during profound hypothermia.

Methods

Fourteen mongrel dogs of either sex weighing 18-25 kg were randomized into lidocaine (LGRP *n* = 6), and control groups (CGRP *n* = 6): one dog was used as a sham operation and another as a normal control. Anaesthesia was induced with 25-30 mg·kg⁻¹ thiopentone 5% and tracheal intubation was facilitated by 2 mg pancuronium which was repeated every hour, 1-2 mg, throughout the experiment. Anaesthesia was maintained with enflurane 1-2% according to surgical requirements.

The left femoral artery was catheterized for arterial blood pressure monitoring and blood samples were periodically drawn for haemoglobin and blood gas analysis (radiometer ABL-3). Heparin (3 mg·kg⁻¹) was administered through the arterial line when required. Arterial blood gas analysis used an alpha stat protocol. The right femoral artery was catheterized for the administration of oxygenated blood during closed thoracic cardiopulmonary bypass (CTCPB). A central venous catheter was placed via the left external jugular vein for monitoring central venous pressure (CVP). A polyperforated catheter was inserted under ECG monitoring into the right atrium via the right external jugular vein for drainage of venous blood during CTCPB. Another venous catheter was inserted distally towards the transverse sinus for blood sampling to determine lactate concentration.

The oxygenator reservoir was primed with hydroxyethyl starch 6% in 250 ml normal saline, 100 ml sodium bicarbonate 5%, 80 ml mannitol 20% and supplemented with Ringer's lactate solution to a volume calculated according to the following equations:

$$\text{diluted haemoglobin} = \frac{\text{blood volume} \times \text{initial haemoglobin}}{\text{priming volume} + \text{blood volume}} \times 100 \text{ percent}$$

$$\text{priming volume} = \frac{80 \text{ ml} \times \text{body weight} \times \text{initial Hb}}{\text{diluted Hb}} \times 100\% (80 \text{ ml} \times \text{body weight})$$

Arterial blood pressure, ECG and heart rate were continuously recorded (Sanei-361) and nasopharyngeal, tympanic and rectal temperatures were monitored simultaneously throughout the experiments. After insertion of the intravascular cannulas, surface cooling with a circulating cooling pad and ice packs was carried out to a rectal temperature of about 30°C and then, after heparinization, the animals were subjected to closed chest cardiopulmonary bypass and further cooled to 20°C. Circulatory arrest was achieved by injecting 3 ml 0.5M KCl into the oxygenator and the circulation was stopped for 90 min. In the LGRP, 4 mg·kg⁻¹ lidocaine were injected into the oxygenator two minutes before cardiac arrest and 2 mg·kg⁻¹ at the beginning of reperfusion and rewarming. In the CGRP, the procedure was identical except that an equal volume of normal saline was used instead of lidocaine. The sham operated dog was treated in the same way as the CGRP animals including bypass, cooling and rewarming but without circulatory arrest. The normal control animal was subjected to examination under anaesthesia only. Post-operatively, neurological function was evaluated by means of a standardized neurological deficit scoring system, modified from D'Alecy's method⁷, hourly for the first six hours and then daily for one week (Table I).

On the eighth day, the brain was removed under thiopentone anaesthesia from six dogs (two from LGRP, two from CGRP, one sham operation and one normal control). After fixation with formaldehyde 10%, samples were taken from the frontal cortex, hippocampus and cerebellar cortex. Five micrometer thick paraffin sections were stained with haemotoxalin and eosin and examined by light microscopy. The severity of ischaemic damage was quantified by randomly selecting 100 neurons from each section and grading them into one of three grades: 1) microvacuolation indicative of early ischaemic oedema (MV). 2) minor ischaemic changes (MIC). 3) significant ischaemic changes (SIC).⁸

The concentration of lidocaine in plasma was determined chromatographically (sensitivity = 9.73%, CV = 9.37%)⁹ at two minutes after the first bolus, at the beginning of reperfusion after 90 min of circulatory

FIGURE 1 Comparison of actual base excess (ABE) values between groups during experiment. * $P < 0.05$ vs CGRP. A. base line value; B. CPB for 30 min; C. reperfusion; D. reperfusion for 30 min; E. reperfusion for 60 min.

FIGURE 2 Intragroup comparison of lactate values in blood from internal jugular vein.

† $P < 0.01$ vs base line value of CGRP; * $P < 0.05$, † $P < 0.01$ vs base line value of LGRP.

A. base line value; B. CPB for 30 min; C. before arrest; D. reperfusion; E. reperfusion for 30 min; F. reperfusion for 60 min.

arrest, and at 2, 30, 60 min after the second bolus. Pharmacokinetic parameters were calculated by using one-compartment model. The lactate and glucose concentrations were measured by using enzymatic methods.^{10,11}

Results are expressed as Mean $\pm$ SD. The STATISTIC program was used to perform the statistical analysis. Lactate, ABE and dextrose values were compared by applying one way ANOVA, and the background parameters, the temperature variables, the duration of each stage and NDS by using T test. Differences were considered significant when the P values were < 0.05 .

FIGURE 3 Comparison of dextrose concentrations between groups. * < 0.05 , † < 0.01 vs LGRP. A. base line value; B. CPB for 30 min; C. before arrest; D. reperfusion; E. reperfusion for 30 min; F. reperfusion for 60 min.

FIGURE 4 Comparison of neurological deficit score between groups in the post-CPB.

* $P < 0.05$ vs LGRP

† $P < 0.01$ vs LGRP

Results

The baseline parameters were similar for the two groups (Table II). The temperatures during the various phases of the study are shown in Table III and the duration of surface cooling and core cooling is shown in Table IV. There were no differences between the groups.

The base excess was higher in the lidocaine group at 30 min after reperfusion and at all subsequent measurement periods (Figure 1). Lactate concentrations increased throughout the study in both groups and was different from baseline at the time of reperfusion

TABLE I Neurological function deficit scoring system (NDS) scale

Neurological item	score	neurological	score	neurological item	score
<i>Consciousness</i>		<i>Cranial nerves</i>		<i>Respiration</i>	
normal	0	corneal reflex	5	normal	0
light coma	15	pupillary light		spontaneous slow	
deep coma	20	reflex	5	regular respiration+	
subtotal	20	swallowing reflex	5	mechanical assistance	10
<i>Motor function</i>		tympanic reflex	5	slow irregular respiration	
walks spontaneously	0	subtotal	20	+mechanical assistance	15
stands spontaneously	5	<i>Pain reflex</i>		apnea	20
sits spontaneously	10	front leg	10	subtotal	20
muscle with normal		hind leg	10		
tension	15	subtotal	20		
muscle without					
tension	20				
subtotal	20				
Total	100				

Note: The total neurological deficit score is the sum of the score from each of the five categories; the maximum deficit score is 100; the minimum score is zero (0) indicating that no scored deficit could be detected.

TABLE II Background parameter values of the two groups (n = 6, M ± SD)

	CGRP	LCGRP	P
Body weight (kg)	19.66 ± 1.25	19.83 ±	0.87
Rectal temperature (°C)	36.5 ± 1.27	37.3 ± 1.17	0.26
Hb (g·dl ⁻¹)	14.38 ± 1.50	14.63 ± 3.03	0.88
PaO ₂	400 ± 82	344 ± 134	0.46
PaCO ₂	36.68 ± 7.01	34.64 ± 4.01	0.40
ABE	-3.46 ± 1.33	-3.08 ± 1.72	0.69
Glucose	98.24 ± 18.04	105.86 ± 78.69	0.89

CGRP for control group

LCGRP for lidocaine group

in the control group and at 30 min after reperfusion in the lidocaine group (Figure 2). Plasma dextrose concentrations increased above baseline in the control group by 30 and 60 min of reperfusion while there was no increase in the lidocaine group (Figure 3).

There were no differences in the neurological deficit score between the groups in the first six post-operative hours (Figure 4). However, from the 12th hour, the neurological deficit score of the lidocaine group was less than that of the control group (Figure 4).

In terms of general behaviour, in the control group, two animals were ataxic, one animal leaned against the wall, three animals needed to be fed and three vomited persistently on the second post-operative day. In the lidocaine group, only one animal was ataxic, one animal had poor mobility and no animals vomited.

The pathological changes are indicated on Table V. There were no differences between the groups in the cerebral cortex. However, in the hippocampus,

regions CA1 and CA4, and the cerebellum there were only mild or no ischaemic changes seen in the lidocaine group whereas in the control group there were considerable changes in these areas (Table V).

The concentrations of lidocaine at each stage of the study and the pharmacokinetic parameters are indicated on Table VI and VII. Hypothermia and circulatory arrest resulted in the $t_{1/2}$ (half life time) of the first bolus being more than twice as long as that of the second bolus.

Discussion

The major findings in this study were that lidocaine given immediately before and after hypothermic circulatory arrest improved post-operative neurological function. This was associated with improved base excess and blood glucose concentrations on reperfusion and improved histopathology.

The dose of lidocaine was based on results of previous experiments in which we demonstrated the cerebral protective effects of lidocaine¹² and the ED₅₀-ED₈₀ were 1.2 - 4.15 mg·kg⁻¹. We therefore used 4 mg·kg⁻¹ as the initial (pre-circulatory arrest) dose. This dose was given two minutes before arrest to allow sufficient time for circulation and drug fixation in the well perfused organs such as the brain, heart, and liver. As it was anticipated that the metabolism of lidocaine would be decreased at 20°C, the second bolus given at the time of reperfusion was reduced to 2 mg·kg⁻¹. This expectation was verified as the first peak plasma concentration was 14.2 ± 3.4 µg·kg⁻¹ and 90 min later, although the plasma level had declined, it was still 3.3 ± 1.4 µg·kg⁻¹ which is within the effective concentration, 1.5 - 5.2 µg·kg⁻¹, of our previous

TABLE III The temperature variables (°C) during CPB (n = 6, M ± SD)

	C GRP		L GRP		P	
	rectal	tym.	rectal	tym.	rectal	tym.
base value	36.77 ± 1.26	35.22 ± 0.92	36.92 ± 1.24	35.73 ± 0.43	> 0.05	> 0.05
CPB on	28.10 ± 1.30	29.30 ± 4.14	30.0 ± 3.23	29.27 ± 3.30	> 0.05	> 0.05
Arrest	19.13 ± 0.36	18.65 ± 1.43	19.37 ± 0.99	17.37 ± 1.90	> 0.05	> 0.05
reperfusion	18.23 ± 1.26	17.65 ± 1.16	18.25 ± 1.07	16.45 ± 2.54	> 0.05	> 0.05
CPB off	34.55 ± 0.37	33.97 ± 1.87	34.32 ± 0.35	31.37 ± 3.71	> 0.05	> 0.05

CGRP for control group

LGRP for lidocaine group

TABLE IV The duration of each stage of CPB (min)(n = 6, M ± SD)

	CGRP	LGRP	P
surface cooling	117 ± 39	136 ± 22	0.05
core cooling	35 ± 10	39 ± 11	0.05
total CPB	100 ± 25	105 ± 24	0.05

CGRP for control group

LGRP for lidocaine group

studies.^{12,13} Our previous study using 3H labeled lidocaine tracer showed that lidocaine was rapidly distributed to areas of the brain vulnerable to ischaemia such as the hippocampus and cortex.¹⁴

Base excess is an index of metabolic acidosis, and the higher base excess values and the lesser changes in lactate in the lidocaine group may be explained by metabolic depression effects of lidocaine, which may have reduced lactate production and, thereby, the magnitude of the acidosis.

Blood glucose concentrations were 2.2 and 2.6 times higher at 30 and 60 min reperfusion in the control group than in the lidocaine group. Both groups received the same intravenous fluid, Ringer's lactate 2000-2500 ml. This difference may have been due to lidocaine depression of the metabolic reaction to stress. Lactate concentrations in both groups increased

steadily after reperfusion but the levels became significantly different from baseline 30 min later in the lidocaine group than in the control group. The more rapid increase in lactate in the control group may be explained by the higher blood sugar levels after reperfusion in the control group.¹⁵

The pathological changes tended to be worse in the cerebellum of the control animals than in the lidocaine group and this may explain the higher incidence of ataxia in the control group.

Lidocaine is a drug well known to clinicians. Our study shows that lidocaine in a dose commonly used clinically for the treatment of arrhythmias improves neurological outcome after hypothermic circulatory arrest in dogs. These results suggest that clinical trials in other species including humans should be considered.

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TABLE V The results of pathology (cells number/100)

	Cortex			Hippocampus CA1			Hippocampus CA4			Cerebellum		
	MV	MIC	SIC	MV	MIC	SIC	MV	MIC	SIC	MV	MIC	SIC
normal control	3	10	0	5	1	0	0	0	0	0	20	0
sham operation	0	15	3	6	2	0	8	6	0	0	5	0
CGRP	3	10	20	5	10	20	5	10	15	0	20	5
CGRP	0	20	30	5	10	0	3	10	40	10	50	10
LGRP	0	20	0	10	0	0	0	10	0	0	0	0
LGRP	0	50	10	10	0	0	10	5	0	10	5	0

MV (microvacuolation) indicates the early stage of postischaemic neuronal edema

MIC (mild ischaemic changes)

SIC (significant ischaemic changes)

CGRP for control group

LGRP for lidocaine group

TABLE VI The concentration of lidocaine in plasma ($\mu\text{g}\cdot\text{ml}^{-1}$) ($n = 6$)

#	The first bolus, 4 $\text{mg}\cdot\text{kg}^{-1}$ ($20 \pm 19 \pm 2^\circ\text{C}$)		The second bolus, 2 $\text{mg}\cdot\text{kg}^{-1}$ ($19 \pm 2 - 34 \pm 2^\circ\text{C}$)		
	2 min	92 min	2 min	30 min	60 min
1	19.0	6.0	14.0	5.8	1.0
2	13.6	2.9	13.2	4.8	2.3
3	11.7	2.0	9.6	2.2	1.9
4	14.6	2.9	18.2	2.3	1.8
5	16.5	3.8	16.6	2.5	3.6
6	9.6	2.4	7.4	1.4	1.4
M $\pm$ SD	14.2 $\pm$ 3.4	3.3 $\pm$ 1.4	13.24.1 $\pm$ 4.1	3.21.7 $\pm$ 1.7	2.0 $\pm$ 0.9

note: The first bolus was given two minutes before circulatory arrest

The second bolus was given at the beginning of reperfusion, 92 min after the first bolus

TABLE VII The pharmacokinetic parameters of lidocaine during CTCBP and circulatory arrest with deep hypothermia ($n = 6$)

No	First bolus, 4 $\text{mg}\cdot\text{kg}^{-1}$ ($20 - 19^\circ\text{C}$)		Second bolus, 2 $\text{mg}\cdot\text{kg}^{-1}$ ($19 - 34^\circ\text{C}$)	
	K min^{-1}	$t_{1/2}$ (min)	K min^{-1}	$t_{1/2}$ (min)
1	0.013	53.308	0.046	15.065
2	0.018	38.500	0.030	23.100
3	0.020	34.650	0.028	24.750
4	0.018	38.500	0.039	17.769
5	0.022	31.500	0.026	26.650
6	0.015	46.200	0.028	24.750
M $\pm$ SD	0.018 $\pm$ 0.003	40.44 $\pm$ 7.996	0.033 $\pm$ 0.007	22.014 $\pm$ 4.560

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