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The Effects of Lidocaine on the Whole Body Distribution of Radioactively Labeled Microspheres in the Conscious Rat

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Radioactively labeled 15-μm microspheres were used to evaluate the effects of intravenous lidocaine on cardiac output and distribution of tissue blood flow in awake rats. After a one-hour control period, all animals (n = 22) received ^{85}Sr-labeled microspheres for a control measurement. The animals were then divided into three groups. The control group (n = 6) received a bolus of saline and then an infusion of saline. After 40 minutes, a second microsphere (^{141}Ce) was injected, the animals killed, and tissue blood flow determined. A second group of rats (n = 8) were similarly treated except that they received a bolus and infusion of lidocaine resulting in a plasma concentration of 1.98 ± 0.3 μg of lidocaine/ml. A third group of rats (n = 8) received a higher dose of lidocaine which resulted in a plasma concentration of 6.37 ± 0.3 μg of lidocaine/ml. In the control and low-dose lidocaine group, there were no changes in blood pressure, heart rate, cardiac output or tissue blood flow. At the higher lidocaine concentration, blood pressure remained the same but cardiac output and heart rate were decreased. Tissue blood flow to brain, heart and muscle was responsible for the increased peripheral resistance. These results suggest that high blood concentrations of lidocaine alter flow to vital organs in the rat. (Key words: Anesthetics, local: lidocaine. Measurement techniques: regional blood flow.)

THE LOCAL ANESTHETIC LIDOCAINE is widely used by anesthesiologists for regional anesthesia and for the control of ventricular dysrhythmias. The drug is also being used intravenously to supplement general anesthesia and more recently to control intracranial pressure.[1,2] In each of these situations, low concentrations of the drug are present in the circulation. While several investigators have studied the effects of lidocaine on individual organ blood flow at low concentrations of lidocaine,[3,4] there are little data available on the effects of high plasma concentrations of lidocaine. High blood concentrations of the drug do occur when bolus doses of the drug are given or when large doses of the drug are given inadvertently.

This study, therefore, was undertaken to evaluate the effects of lidocaine on hemodynamics and organ blood flow. Two concentrations of lidocaine, which are seen clinically, were examined. The radioactive microsphere technique was used because it allows for the determination of cardiac output and distribution of blood flow in the entire animal before and after drug treatment.

Methods

Twenty-two fasted Wistar rats (230–360 g) were anesthetized with diethyl ether and PE-50 polyethylene tubing was inserted into the left ventricle via the right carotid artery utilizing pressure monitoring as a guide. PE-50 tubing was also inserted into the left femoral artery and vein. Both incisions were closed and the catheters flushed with a solution of heparin and 0.9 per cent saline. The rats were then placed in restraining cages and allowed to awaken for one hour before experiments were begun. Blood pressure was monitored continuously through the femoral artery cannula by a Statham P23 Db pressure transducer using a Brush Mark 260 recorder.

The protocol consisted of a one-hour control period, followed by a bolus injection and 40-min infusion of either saline or lidocaine. The animals were divided into three groups. The first group (n = 8) received a bolus of 250 μg of lidocaine over 30 s followed by an infusion of 75 μg/min. The second group (n = 8) received a bolus of 750 μg followed by an infusion of 250 μg/min. A 40-min infusion period was chosen because stable concentrations of lidocaine could be obtained. In humans, bolus and then an infusion of lidocaine produce stable levels within 25 min.[5] In the rat, levels would approach equilibrium at a more rapid rate. Previous work from our laboratory has shown that after 15 min, plasma

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concentrations of lidocaine are stable using the bolus and then infusion technique.[6] A control group (n = 6) was treated identically but received only saline. The bolus of lidocaine or saline was given as a total volume of 0.375 ml. The infusion rate was 20 μl/min.

To determine cardiac output and distribution of blood flow, carbonized 15-μm labeled Strontium-85 (^{85}Sr) and Cerium-141 (^{141}Ce) microspheres were used as we have previously described.[7] The microspheres had been suspended in Dextran 10 per cent, containing Tween 80®, 0.5 per cent. The microspheres were agitated and 0.1–0.2 ml of the microsphere mixture (40,000–80,000 microspheres) were drawn into a tuberculin syringe which had been modified to fit into a gamma counting vial. The loaded syringes were then counted in a Beckman® Biogamma counter at the appropriate energy spectrum for each isotope. At the end of the awake control period, the ^{85}Sr microspheres were again agitated, then injected into the left ventricular catheter over 20 s and flushed with 0.4 ml of normal saline. Ten seconds prior to the microsphere injection and for the following 60 s, blood was withdrawn from the femoral artery by a constant withdrawal Gilford® pump for the determination of cardiac output. The blood (approximately 0.7 ml) was then placed in a pre-weighed counting vial and its weight determined. The empty injection syringe was again counted. The same procedure was done with the ^{141}Ce microspheres at the end of the saline or lidocaine infusion period. Arterial blood (0.2 ml) for blood-gas analysis was obtained after each microsphere injection. Arterial blood was also obtained after the second microsphere injection for determination of plasma lidocaine level by gas chromatography. The animals were then killed, the organs of the body dissected out, weighed and placed in counting vials. Aliquots of skin, muscle, liver, and small bowel were used, otherwise the entire organ was placed in the counting vial. The entire liver and small bowel were weighed. Contributions to body weight of skin and muscle were taken as 18 per cent and 45 per cent respectively.[8] The tissues and blood for cardiac output determination were then counted in the gamma counter at the appropriate energy spectra taking into account overlap of ^{85}Sr in the ^{141}Ce window.

Cardiac output was determined by the formula: cardiac output = counts injected × reference sample withdrawal rate ÷ reference blood counts. Regional blood flow in $ml \cdot min^{-1} \cdot g^{-1}$ tissue was determined by multiplying the cardiac output by the percentage of individual microspheres in the individual tissue and dividing by the weight of the tissue.

The data presented are expressed as the mean ± SE of the mean. The data for all of the 22 rats for the first microsphere injection were compared to the data obtained after the second microsphere injection. The data were analyzed using Student's t test for unpaired data. $P < 0.05$ was taken as significant.

Results

In the control group there were no significant differences in cardiac output or tissue blood flow using the two different microsphere labels 40 min apart (table 1). The control arterial blood-gas values were $Pa_{O_2} = 81 \pm 2$ torr, $Pa_{CO_2} = 32 \pm 1$ torr, and $pH = 7.41 \pm 0.01$.

In the animals receiving the lower lidocaine dose, the mean lidocaine concentration at the end of the infusion was 1.98 ± 0.27 μg/ml. Cardiac output, heart rate, mean arterial pressure, tissue blood flow, and arterial blood-gas values showed no significant change from the control values. There was a tendency for muscle blood flow to decrease but this did not reach statistical significance (table 1).

In the animals receiving the higher lidocaine dose, the mean plasma lidocaine concentration at the end of the infusion period was 6.37 ± 0.29 μg/ml. Animals in this group had significant decreases in cardiac output and heart rate ($P < 0.05$). The animals appeared sleepy but were easily aroused. Mean arterial pressure was not significantly changed, despite the decline in cardiac output and was maintained by an increase in systemic vascular resistance. Blood flow in $ml \cdot min^{-1} \cdot g^{-1}$ tissue was decreased significantly in brain, heart, and muscle. Renal and intestinal flow were maintained despite the reduction in cardiac output (table 1). Arterial blood-gas values were $Pa_{O_2} = 81 \pm 2$ torr, $Pa_{CO_2} = 33 \pm 1$ torr, and $pH = 7.40 \pm 0.02$.

Discussion

The hemodynamic effects of lidocaine have been examined by a number of investigators in both humans and experimental animals. In patients with a variety of heart diseases in whom 1–2 mg/kg of intravenous lidocaine was administered, Jewett *et al.*,[9] Grossman *et al.*,[10] and Harrison *et al.*[11] found no significant changes in hemodynamic parameters. While these authors did not measure plasma concentrations of lidocaine, such doses result in approximately 2 μg/ml in adults. Wiklund,[3] who did measure plasma concentrations, noted slight increases in heart rate, mean arterial pressure, and cardiac output in healthy volunteers receiving lidocaine infusions with plasma concentrations of 2.4 μg/ml. At similar lidocaine concentrations, Klein *et al.*[4] noted increases in mean

TABLE 1. Hemodynamic and Blood Flow Alterations before and after Intravenous Lidocaine

	Control (n = 22)	2nd Control (n = 6)	Low-dose Lidocaine (n = 8)	High-dose Lidocaine (n = 8)
Mean arterial pressure (torr)	117 ± 4	123 ± 4	116 ± 2	112 ± 2
Heart rate (bpm)	454 ± 6	463 ± 6	462 ± 4	371 ± 8*
Cardiac output (ml/min)	170 ± 7	156 ± 16	172 ± 15	108 ± 12*
Blood flow ($ml \cdot min^{-1} \cdot g^{-1}$)				
Brain	1.11 ± 0.05	1.33 ± 0.12	1.05 ± 0.04	0.62 ± 0.05*
Heart	8.62 ± 0.81	7.26 ± 0.63	8.16 ± 0.47	4.89 ± 0.52*
Lung	1.04 ± 0.13	0.94 ± 0.29	0.93 ± 0.15	1.05 ± 0.18
Skin	0.22 ± 0.02	0.20 ± 0.01	0.24 ± 0.02	0.14 ± 0.03
Kidneys	14.73 ± 0.85	13.41 ± 2.63	15.04 ± 1.09	13.20 ± 1.30
Muscle	0.26 ± 0.03	0.22 ± 0.07	0.20 ± 0.02	0.10 ± 0.01*
Liver	0.37 ± 0.04	0.27 ± 0.05	0.37 ± 0.07	0.36 ± 0.06
Spleen	1.77 ± 0.14	2.08 ± 0.45	2.22 ± 0.34	1.91 ± 0.31
Small intestine	1.29 ± 0.10	1.36 ± 0.28	1.48 ± 0.17	1.36 ± 0.14
Large intestine	0.84 ± 0.08	0.99 ± 0.23	0.99 ± 0.11	0.77 ± 0.14
Stomach	0.81 ± 0.07	0.65 ± 0.08	1.07 ± 0.12	0.64 ± 0.11*

* Significant differences ($P < 0.05$) between the values for high-dose lidocaine and the control group.

arterial pressure and systemic vascular resistance with no change in cardiac output in patients with coronary artery disease or valvular heart disease. These studies performed in the rat provide results which are compatible with what is known to occur in humans.

In the present study, higher concentrations of lidocaine resulted in significant changes in heart rate and cardiac output. Whether all of the tissue blood flow changes can be ascribed to the decrease in heart rate alone seems unlikely. In our previous publication,[7] halothane and enflurane decreased heart rate to a similar degree, and also there were significant differences in distribution of blood flow to various tissues between these two anesthetics.

The use of the laboratory rat to draw inferences to humans must be made with caution. Our previous study did show that the rat showed many hemodynamic similarities to humans when halothane or enflurane anesthesia was administered. Conclusions from studies using experimental animals such as rats, dogs, or even monkeys must eventually be shown to be true in humans. However, at the present time, techniques to measure whole body distribution of blood flow in humans are not available and experimental animals must be used to obtain such data.

The higher concentration of lidocaine resulted not only in significant changes in heart rate and cardiac output but decreased blood flow to heart, stomach, brain, and muscle. The 33 per cent decrease seen in myocardial blood flow could be secondary to the decreased metabolic demands of the heart associated with the 18 per cent decline in heart rate. Knight and coworkers[12] administered lidocaine intravenously to patients undergoing cardiac surgery. They also found that at plasma lidocaine levels of 6.43 μg/ml there was a decrease in cardiac output and left ventricular stroke work. This would support the concept that the decreased myocardial blood flow is secondary to decreased demand.

Brain blood flow decreased due to an increase in cerebral vascular resistance at the higher concentration of lidocaine. When a similar fall in cardiac output and heart rate was obtained using halothane anesthesia, brain blood flow increased. The mechanism whereby lidocaine decreases brain blood flow at these lidocaine concentrations is unknown. Carbon dioxide concentration did not change from the control state. Sakabe *et al.*[13] noted decreases in brain oxygen consumption and blood flow in dogs, albeit at larger doses of lidocaine levels than ours. This decrease in brain blood flow may explain the attenuation of intracranial pressure rises seen when endotracheal tube suctioning is preceded by intravenous lidocaine.[2]

Although the cardiac output decreased 35 per cent at the higher lidocaine level, mean arterial pressure was maintained by an increase in systemic vascular resistance. The largest part of this increase occurred in striated muscle which comprises 45 per cent of rat body mass. As mean arterial pressure was not changed, any alteration in blood flow was secondary to changes in vascular resistance. Whether these changes are a direct effect of lidocaine or secondary to some other factor is not clear. Although lidocaine is generally thought of as vasodilating and indeed at high concentrations it relaxes all vascular smooth muscle, it is not surprising that it might constrict some vascular beds. Lidocaine has been shown *in vitro* to increase both the basal tone and spontaneous contractions in isolated rat portal vein.[4] It will also initially enhance contraction of arterioles in rat mesocecum induced by catecholamines.[15] Hyman[16] has shown that in dogs, lidocaine can cause pulmonary venous con-

striction *in vivo*, while Cibils[17] demonstrated *in vitro* that lidocaine caused constriction of human uterine arteries taken from pregnant women. A small decrease in blood flow to the stomach was observed in these experiments but other splanchnic beds did not show such decreases. At a plasma concentration of 2.1 μg/ml, Benowitz *et al.*,[18] employing 50-μm microspheres, noted a significant decrease of 21 per cent in blood flow to striated muscles. At similar lidocaine concentrations, in our study, there was a tendency for a decrease in blood flow but at 6.4 μg/ml, a 50 per cent reduction in muscle blood flow was observed.

In summary, we were not able to demonstrate any significant hemodynamic changes at a lidocaine level of approximately 2 μg/ml. At higher levels (6.4 μg/ml) significant reductions in cardiac output and heart rate occurred as did alterations in tissue blood flow, while systemic arterial pressure was maintained by vasoconstriction especially in skeletal muscle.

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