

Lidocaine Constricts or Dilates Rat Arterioles in a Dose-dependent Manner

Roger A. Johns, M.D.,* Cosmo A. DiFazio, M.D., Ph.D.,† David E. Longnecker, M.D.‡

The microvascular effects of varying concentrations of lidocaine were evaluated with the use of videomicroscopy in an *in vivo* rat cremaster muscle preparation. Animals were anesthetized with chloralose and urethane and breathed room air spontaneously. Mean arterial pressure and heart rate were measured via a carotid artery cannula. The cremaster muscle was suffused with a balanced electrolyte solution and pH, temperature, P_{O_2} , P_{CO_2} , and osmolarity were controlled. Internal diameters of fourth-order arterioles in the cremaster muscle were measured with an electronic vernier system. In one group of animals ($n = 7$), arteriolar diameters were measured every 30 s during a 10-min control period, a 10-min period of topical application of lidocaine hydrochloride, and a 10-min recovery period. Lidocaine hydrochloride, 10^0 , 10^1 , 10^2 , 10^3 , or $10^4 \mu\text{g} \cdot \text{ml}^{-1}$, produced changes in arteriolar diameters to 88.9 ± 0.9 , 79.0 ± 1.3 , 67.5 ± 2.4 , 60.1 ± 3.4 , and 127.1 ± 7.2 per cent of control, respectively ($P < 0.001$). In a second group of animals ($n = 4$), fourth-order arteriolar diameters were measured during administration of intravenous lidocaine, $1.2 \text{ mg} \cdot \text{kg}^{-1}$ bolus plus $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Vasoconstriction to $91.3 \pm 0.9\%$ of control was observed ($P < 0.001$). These results demonstrate a biphasic dose-dependent response to lidocaine. At lesser concentrations, including those that occur in the plasma of patients during intravenous infusion or nerve blocks, dose-related vasoconstriction occurred. Lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$, a concentration similar to that which occurs at the site of injection during infiltration, nerve block, or epidural anesthesia, produced vasodilation. It appears likely that the observed effects are a result of peripheral rather than central actions of the drug. (Key words: Anesthetics, local: lidocaine. Arteries: arterioles; microcirculation. Microcirculation: arterioles.)

REPORTS of the peripheral vascular effects of local anesthetics are confusing, since they contain evidence for both vasodilating and vasoconstricting actions of these drugs.¹ Most assessments of vasoactivity have employed indirect methods, such as calculations of regional vascular resistances,² or crude measurements, such as the degree of skin blanching after local infiltration.³ Others have involved isolated preparations such as strips of vascular smooth muscle; and, in most instances, only one or two concentrations of drug were tested.

A definition of the microvascular actions of local anesthetics would be of value in understanding the systemic circulatory effects of these drugs, as well as in evaluating their absorption from various sites of injection. Therefore, we investigated the dose-related effects of

lidocaine on fourth-order arteriolar diameters with the use of an *in vitro* preparation that allowed direct observation of the microvasculature in the cremaster muscle of the rat and that permitted us to obtain data for widely varying doses of the drug.

Methods

Male Sprague-Dawley rats ($160 \pm 5 \text{ g}$) were anesthetized with chloralose, $60 \text{ mg} \cdot \text{kg}^{-1}$, plus urethane, $800 \text{ mg} \cdot \text{kg}^{-1}$, intraperitoneally. This combination has been shown to have minimal effects on systemic hemodynamics and microvascular responses in the rat.^{4,5} The animals breathed room air spontaneously through a tracheostomy. Rectal temperature was measured continuously and maintained at 37°C by a heat lamp. Mean arterial pressure was recorded continuously from a catheter in the left common carotid artery. Heart rate, obtained from the phasic arterial pressure tracing, was recorded at 5-min intervals.

The left cremaster muscle was exposed through a midline scrotal incision and prepared for observation of the microvasculature according to the technique of Baez.⁶ The rat was placed on a platform; and the muscle, with nerves and vessels intact, was spread over a heated transparent pedestal. The whole preparation then was mounted on the stage of a compound microscope. A warmed, buffered balanced salt solution (containing in mM: NaHCO_3 , 25.5; NaCl , 131.9; KCl , 4.7; CaCl_2 , 2.0; MgSO_4 , 1.17) with or without lidocaine, continuously was suffused over the muscle at a constant flow rate of $1.5 \text{ ml} \cdot \text{min}^{-1}$. The pH of all suffusion solutions was controlled at a value of 7.2 throughout. When lidocaine was added to the balanced salt solution, the electrolyte concentration was decreased slightly so as to maintain constant osmolarity. The suffusion solution was equilibrated with 95% nitrogen and 5% CO_2 to maintain a constant P_{CO_2} and to provide a surface oxygen tension similar to that within the muscle, since increased oxygen tension has been shown to alter the microvasculature.⁷ Cremaster muscle temperature was measured continuously and maintained at $34\text{--}35^\circ \text{C}$, the physiologic temperature of the rat scrotum.⁸ The microscopic image was displayed continuously on a video monitor (total magnification, $\times 625$) equipped with an electronic vernier,‡ which was used to measure internal vessel diam-

* Resident in Anesthesiology.

† Professor of Anesthesiology.

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Address reprint requests to Dr. Johns.

‡ Circon Corporation, Santa Barbara, California 93111.

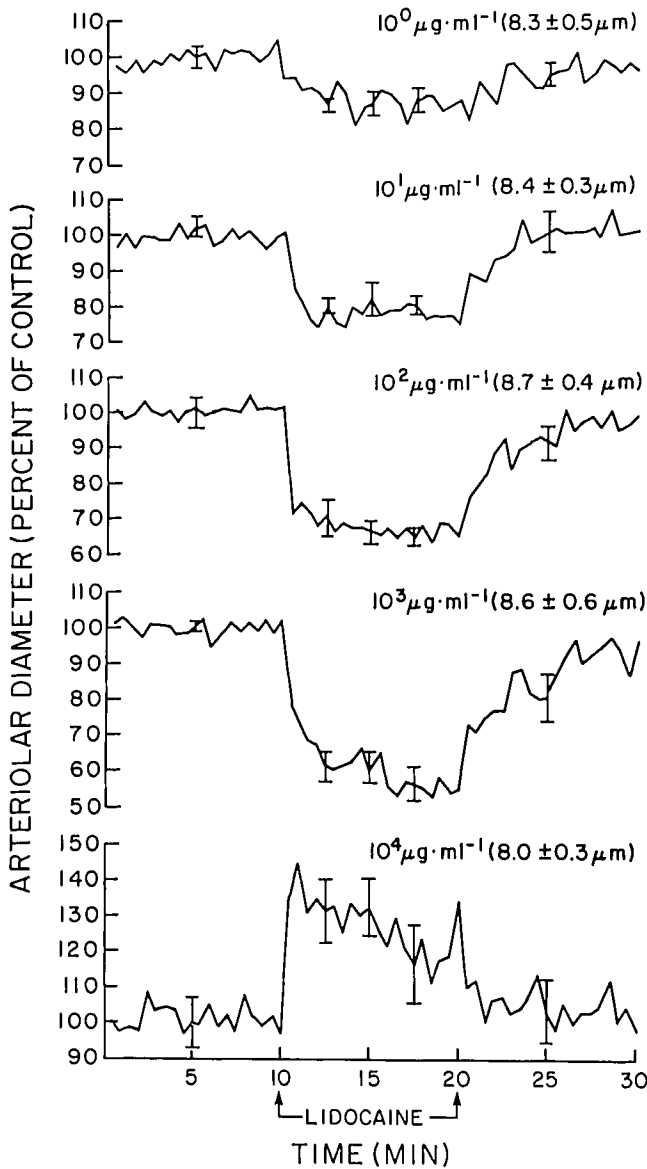


FIG. 1. The time course of arteriolar response to topical lidocaine. Values in parentheses represent average control diameters (\pm SEM). Significant ($P < 0.001$) constriction occurred at 10^0 , 10^1 , 10^2 , and $10^3 \mu\text{g}\cdot\text{ml}^{-1}$ ($n = 8$ for each group) and significant ($P < 0.025$) dilation at $10^4 \mu\text{g}\cdot\text{ml}^{-1}$ ($n = 4$).

eters at 30-s intervals throughout all experiments. System accuracy was $\pm 0.5\%$. The preparation then was allowed to stabilize for 1 h prior to beginning experiments in order to minimize the effects of tissue manipulation on microvascular diameters.

The cremasteric microvasculature consisted of a series of branchings of arterioles and venules from central vessels, and each successive branching was defined as a specific "order" of artery or vein. Fourth-order arterioles were chosen for study because these precapillary arterioles are the major site of vascular resistance in the

peripheral circulation and because they are the most responsive of the microvessels to vasoactive stimuli.^{9,10}

In the experiments involving topical drug administration, the cremaster was suffused continuously with balanced salt solution with or without lidocaine. The protocol consisted of three 10-min intervals: a control period, a topical lidocaine administration period, and a recovery period. Lidocaine hydrochloride monohydrate was applied in one of five concentrations: 10^0 , 10^1 , 10^2 , 10^3 , or $10^4 \mu\text{g}\cdot\text{ml}^{-1}$ (3.46×10^{-6} to 3.46×10^{-2} M, respectively). Lidocaine, 10^0 , 10^1 , 10^2 , and $10^3 \mu\text{g}\cdot\text{ml}^{-1}$, was applied to seven animals, and lidocaine, $10^4 \mu\text{g}\cdot\text{ml}^{-1}$, to four animals.

In the experiments involving the intravenous administration of lidocaine, the protocol consisted of two 45-min intervals: a saline infusion followed by a saline with lidocaine infusion. The lidocaine was administered as a $1.2 \text{ mg}\cdot\text{kg}^{-1}$ bolus followed by $0.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in each of four rats.

Saline, or saline plus lidocaine, was infused via the left femoral vein at a flow rate of $20 \mu\text{l}\cdot\text{min}^{-1}$. Arteriolar diameters were measured only during the final 15 min of each interval because previous studies demonstrated that 15–30 min were required for plasma lidocaine concentrations to stabilize when this infusion protocol was used in rats.¹¹

Plasma concentrations of lidocaine were measured by gas chromatography¹² after 10^3 and $10^4 \mu\text{g}\cdot\text{ml}^{-1}$ topical lidocaine applications and after intravenous lidocaine infusion.

Arteriolar diameters were normalized as per cent of control by determining the mean diameter for each control period and then dividing all values by the average control value (ACV). Average data for arteriolar diameters were determined for each measurement interval (30 s), and overall average responses during the 10 min of topical lidocaine application also were calculated. Heart rate and arterial pressure were averaged for both the control and drug application intervals. Arteriolar diameter, mean arterial pressure, and heart rate comparisons were made with the use of paired *t* tests; and $P < 0.05$ was accepted as significant. Values are expressed as the mean \pm the standard error of the mean throughout.

Results

Heart rate and mean arterial pressure were not altered by either topical or intravenous lidocaine. For all groups, heart rate averaged $436 \pm 10 \text{ beats}\cdot\text{min}^{-1}$ during control and $434 \pm 13 \text{ beats}\cdot\text{min}^{-1}$ during lidocaine; mean arterial pressure was $107 \pm 3 \text{ mmHg}$ during control and $105 \pm 3 \text{ mmHg}$ during lidocaine.

A biphasic dose-response relationship was found with

increasing doses of topically applied lidocaine (figs. 1 and 2). Lidocaine, 10^0 , 10^1 , 10^2 , and $10^3 \mu\text{g} \cdot \text{ml}^{-1}$, constricted arterioles to 88.9 ± 0.9 , 79.1 ± 1.3 , 67.5 ± 2.4 and $60.1 \pm 3.4\%$ of control, respectively ($P < 0.001$). Lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$, produced arteriolar dilation to $127.1 \pm 7.2\%$ of control ($P < 0.025$). Plasma lidocaine concentrations averaged $0.60 \pm 0.02 \mu\text{g} \cdot \text{ml}^{-1}$ after lidocaine, $10^3 \mu\text{g} \cdot \text{ml}^{-1}$, and $1.20 \pm 0.16 \mu\text{g} \cdot \text{ml}^{-1}$ after lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$.

During the topical application of lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$, we noted varying degrees of apparent contraction of the cremaster muscle, as well as the appearance of red blood cells in the suffusion solution. In four animals not included in this portion of the study, the muscle contraction resulted in movement of the vessel out of the field of view, such that arteriolar diameters could not be measured.

The intravenous infusion of lidocaine resulted in arteriolar constriction to $91.3 \pm 0.9\%$ of control (fig. 3). The mean plasma lidocaine concentration with intravenous infusion was $3.61 \pm 0.47 \mu\text{g} \cdot \text{ml}^{-1}$.

Discussion

The vascular effects of lidocaine have been evaluated in animals and humans in a variety of experimental

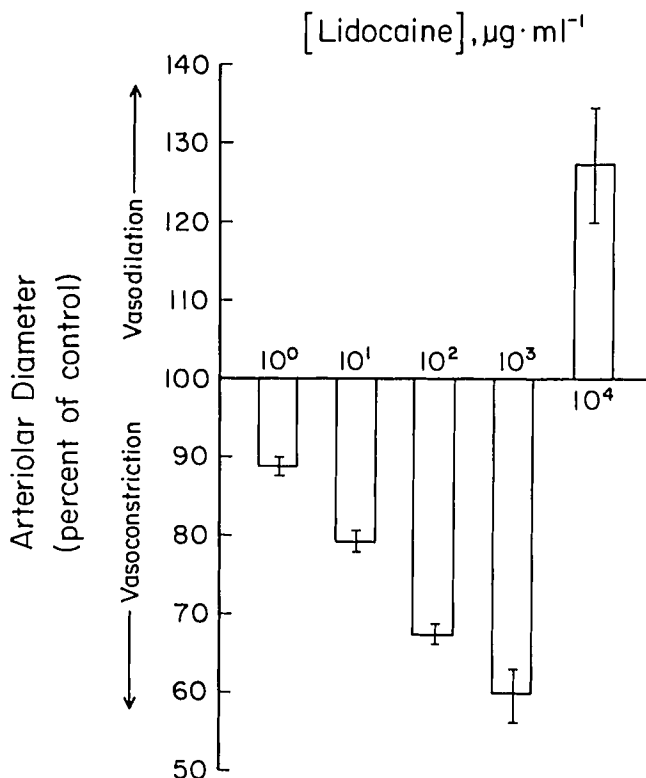


FIG. 2. The average arteriolar diameter (\pm SEM) during each 10-min period of lidocaine application expressed as percentage of the average control value.

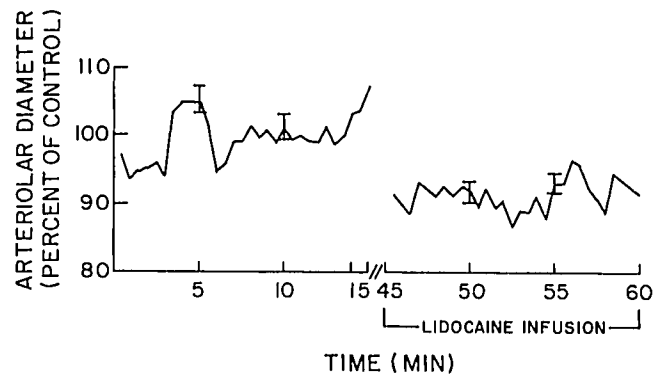


FIG. 3. The vasoconstricting effect (mean \pm SEM; $n = 4$) of intravenous lidocaine infusion (mean plasma levels $3.61 \pm 0.47 \mu\text{g} \cdot \text{ml}^{-1}$) on fourth-order arterioles ($P < 0.001$). Mean control diameter was $9.3 \pm 0.4 \mu\text{m}$.

conditions that have included varying concentrations and dosages, and both systemic and local administrations. The results, however, are confusing, since evidence for both vasoconstriction and vasodilation is reported.

Jorfeldt *et al.*¹³ and Klein *et al.*¹⁴ demonstrated increases in total systemic vascular resistance in man at plasma lidocaine concentrations of $3\text{--}6 \mu\text{g} \cdot \text{ml}^{-1}$, implying that peripheral constriction must have occurred in some vascular beds. Aps and Reynolds³ used the degree of blanching or erythema of the skin after intradermal injection as a crude index of vasoconstriction or vasodilation. Blanching (implying vasoconstriction) occurred with the use of lidocaine, $5 \times 10^3 \mu\text{g} \cdot \text{ml}^{-1}$, while erythema (implying vasodilation) predominated with lidocaine, $2 \times 10^4 \mu\text{g} \cdot \text{ml}^{-1}$. Lescanic *et al.*¹⁵ used radioactively labeled microspheres to demonstrate decreased regional blood flows to the brain, heart, and skeletal muscle of rats during the intravenous infusion of lidocaine. Although they did not calculate regional vascular resistances, systemic arterial pressure did not change while cardiac output decreased, implying an increase in systemic vascular resistance. Astrom¹⁶ reported increased contraction in the isolated rabbit aorta after the application of lidocaine.

Nishimura *et al.*¹⁷ observed increased blood flow in the hind limb of dogs after femoral artery injection of 2% lidocaine, suggesting that vasodilation occurred peripherally. Goldman *et al.*¹⁸ observed vasodilation of the peripheral vessels of the rabbit ear after intradermal injection of 2% lidocaine; and Altura,¹⁹ using video microscopy, observed dilation of rat mesenteric arterioles after application of $2.5 \cdot 10^3 \mu\text{g} \cdot \text{ml}^{-1}$ of lidocaine. Dose-response data were not obtained in these experiments.

In vitro studies that use isolated blood vessels may not be representative of the results that would be obtained *in vivo* because of trauma, isolation from vasoactive substances, and the highly artificial environment of the

tissue. Intravascular administration of vasoactive drugs may produce changes in systemic arterial pressure, resulting in microvascular alterations that are consequent to the change in arterial pressure and, perhaps, independent of any direct peripheral vascular actions of the agents. Many of these potential pitfalls were minimized or eliminated in the present study, which employed topical and intravenous administration of lidocaine to the rat cremaster muscle. Careful control of the solution suffusing the microvascular environment allowed us to obtain results that were independent of changes in temperature, pH, osmolarity, P_{O_2} or P_{CO_2} . The preparation also allowed us to obtain dose-response data in a noncumulative manner.

Our data demonstrated a biphasic dose response to increasing concentrations of topically applied lidocaine. At lesser concentrations, including those that occur in the plasma of patients during intravenous infusion or nerve blocks, dose-related vasoconstriction was observed. Lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$, a concentration similar to that which occurs at the site of injection during infiltration, nerve block, or epidural anesthesia, produced vasodilation.

Animals receiving intravenous lidocaine had plasma concentrations of $3.60 \pm 0.47 \mu\text{g} \cdot \text{ml}^{-1}$ and showed about the same degree of vasoconstriction as did those receiving similar concentrations (10^0 and $10^1 \mu\text{g} \cdot \text{ml}^{-1}$) applied topically. This supports the hypothesis that the vasoconstriction was the result of peripheral rather than central action.

Aps and Reynolds,³ after intradermal injections of lidocaine, $2 \times 10^4 \mu\text{g} \cdot \text{ml}^{-1}$, observed that local hemorrhage often accompanied vasodilation and proposed that the dilation might be secondary to tissue irritation. In a recent review, Covino²⁰ noted that histologic studies have shown skeletal muscles to be particularly sensitive to the irritative effects of local anesthetics. Our observations of cremaster muscle contraction and extravasation of red blood cells may be related to these irritative effects.

In summary, in using an *in vivo* microscopic preparation, we have demonstrated a biphasic response of fourth-order arterioles to increasing concentrations of lidocaine. Progressive constriction occurred with lidocaine concentrations from 10^0 to $10^3 \mu\text{g} \cdot \text{ml}^{-1}$, and vasodilation was observed with lidocaine, $10^4 \mu\text{g} \cdot \text{ml}^{-1}$. Our results suggested that the peripheral circulatory action of lidocaine during systemic concentrations of approximately $3-4 \mu\text{g} \cdot \text{ml}^{-1}$ were the result of local, not central, actions of the drug, because similar peripheral vascular effects were seen when the drug was administered either topically or intravenously.

References

1. Blair MR: Cardiovascular pharmacology of local anaesthetics. *Br J Anaesth* 47(S):247-252, 1975
2. Jorfeldt L, Lofstrom B, Pernow B, Wahren J: The effect of mepivacaine and lignocaine on forearm resistance and capacitance vessels in man. *Acta Anaesthesiol Scand* 14:183-201, 1970
3. Aps C, Reynolds F: The effect of concentration on vasoactivity of bupivacaine and lignocaine. *Br J Anaesth* 48:1171-1174, 1976
4. Delano FA, Zweifach BW: Anesthesia and microvascular dynamics in spontaneously hypertensive rats. *Am J Physiol* 241 (Heart Circ Physiol 10):H821, 1981
5. Weigman DL, Joshua IG, Morff RJ, Harris PD, Miller FN: Microvascular responses to norepinephrine in renovascular and spontaneously hypertensive rats. *Am J Physiol* (Heart Circ Physiol 4):H545-H548, 1979
6. Baez S: An open cremaster preparation for the study of blood vessels by *in vivo* microscopy. *Microvasc Res* 5:348-394, 1973
7. Duling BR: Changes in microvascular diameter and oxygen tension induced by carbon dioxide. *Circ Res* 32:370, 1973
8. Hutchins PM, Goldstone J, Wells R: Effects of hemorrhagic shock on the microvasculature of skeletal muscle. *Microvasc Res* 5:131, 1973
9. Duling BR, Berne RM: Microiontophoretic application of vasoactive agents to the microcirculation of the hamster cheek pouch. *Microvasc Res* 1:158-173, 1968
10. Longnecker DE, Creasy RA, Ross DC: A microvascular site of action of sodium nitroprusside in striated muscle of the rat. *ANESTHESIOLOGY* 50:111-117, 1979
11. DiFazio CA, Niederlehner JR, Burney RG: The anesthetic potency of lidocaine in the rat. *Anesth Analg* 55:818-821, 1976
12. DiFazio CA, Brown RE: The analysis of lidocaine and its postulated metabolites. *ANESTHESIOLOGY* 34:86-88, 1971
13. Jorfeldt L, Lofstrom B, Pernow B, Persson B, Wahren J, Widman B: The effect of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiol Scand* 12:153, 1968
14. Klein SW, Sutherland RIL, Morch JE: Hemodynamic effects of intravenous lidocaine in man. *Can Med Assoc J* 99:472-475, 1968
15. Lescanic ML, Miller ED, DiFazio CA: The effects of lidocaine on the whole body distribution of radioactively labeled microspheres in the conscious rat. *ANESTHESIOLOGY* 55:269-272, 1981
16. Astrom A: Influence of some local anaesthetics upon the adrenaline contraction of isolated strips of rabbit aorta. *Acta Physiol Scand* 60:30, 1964
17. Nishimura N, Morioka T, Sato S, Ruba T: Effects of local anesthetic agents on the peripheral vascular system. *Anesth Analg* 44: 135-139, 1965
18. Goldman V, Killey HC, Wright C: Effects of local analgesic agents and vasoconstrictors on rabbits' ears. *Acta Anaesthesiol Scand* (Suppl) 23:353-365, 1966
19. Altura BM: Chemical and humoral regulation of blood flow through the precapillary sphincter. *Microvasc Res* 3:361-384, 1971
20. Covino BG: Pharmacology of local anesthetic agents, *Seminars in Anesthesia*, vol 2. Edited by Katz RL. New York, Grune and Stratton, 1983, pp 10-23