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An Analgesic Action of Intravenously Administered Lidocaine on Dorsal-horn Neurons Responding to Noxious Thermal Stimulation

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Using extracellular single-unit recording techniques, effects of intravenously administered lidocaine on dorsal-horn nociceptive neurons were studied in cats made decerebrate whose spinal cords had been transected. Thirty-seven neurons in Rexed lamina V responding to high-threshold mechanical and noxious thermal stimuli (radiant heat, using Hardy-Wolff-Goodell dolorimeter) were studied. Lidocaine hydrochloride, 2.5, 5, and 10 mg/kg, iv, produced dose-related suppression of both spontaneous activity and responses of these neurons to noxious thermal stimulation. Spontaneous discharge frequencies at maximum suppression, observed 3–7 min after administration of each of the three doses of lidocaine were 64 ± 14 (mean ± 1 SE), 32 ± 8, and 25 ± 9 per cent of control values, respectively; responses to noxious thermal stimuli were 83 ± 5, 52 ± 8, and 39 ± 7 per cent of the control values, respectively. Threshold skin temperature to noxious thermal stimulation increased from 44.7 ± 0.4 C (control) to 46.3 ± 0.7 C with lidocaine, 5 mg/kg ($P < 0.05$), to 47.8 ± 0.8 C with lidocaine, 10 mg/kg ($P < 0.01$). The times necessary for recovery varied in a dose-related fashion. Plasma lidocaine concentrations 5 min after lidocaine, 5 mg/kg, averaged 3.6 ± 0.7 μg/ml. These data support the clinical impression that intravenously administered lidocaine produces analgesia at plasma concentrations of 3–10 μg/ml. It is suggested that lidocaine may block conduction of nociceptive impulses, at least in part, by suppression of spinal-cord nociceptive neurons. (Key words; Anesthetics, intravenous: lidocaine. Spinal cord: dorsal-horn neurons.)

VARIOUS CLINICAL REPORTS describe the use of local anesthetic agents administered intravenously for the relief of pain and as a supplement to general anesthesia.[1–4] The mechanism by which intravenously administered lidocaine produces analgesia is still unclear, however. Previous studies suggest that lidocaine may decrease the conduction of impulses by the thin myelinated and unmyelinated fibers of peripheral nerves[5,6] and also decrease the amplitude of polysynaptic spinal reflexes.[7,8] However, there has been no report of the effects of intravenously administered local anesthetics on the single-unit activity of spinal nociceptive neurons. The purpose of the present study was to investigate the effects of intravenously administered lidocaine on the activity of spinal neurons responding to peripheral noxious thermal stimulation.

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Methods

Experiments were performed on 37 cats weighing 2.0 to 3.8 kg. During anesthesia with halothane, nitrous oxide, and oxygen, animals were prepared with tracheostomy, carotid arterial cannulation to monitor arterial blood pressure, and jugular vein cannulation for the administration of drugs and intravenous fluids. Both carotid arteries were ligated distally and bilateral decerebrating electrical lesions were made stereotactically in the midbrain reticular formation in order to eliminate the necessity for basal narcosis which may, by itself, depress neuronal activity. Lumbar and sacral cord segments were exposed by laminectomy and covered with a mixture of paraffin and mineral oil maintained at 37 C. The spinal cord was transected at the level of L1. Anesthesia was then discontinued and the animals' lungs were artificially ventilated with oxygen using a Harvard pump. Gallamine triethiodide, 2–3 mg/kg/min, was given intravenously. End-tidal CO_2 was held at 30–37 torr as measured by an infrared gas analyzer. Systolic blood pressure remained above 80 torr and rectal temperature was maintained at 36.5 ± 1.0 C with an infrared heating lamp and a servo-controlled warm-water mattress. The foot pads of the left hind limb, which was fixed with the sole upwards in a holder, were blackened with India ink and a miniature thermistor was placed adjacent to the center of the receptive field. Extracellular unit recording of dorsal-horn neurons was performed near the L7 dorsal root entry zone of the spinal cord using a platinum microelectrode with 1–2-μm exposed tip, which was inserted by a hydraulic micromanipulator. The input signals were processed through an AC preamplifier, displayed on a cathode-ray oscilloscope, and simultaneously recorded on magnetic tape. Neurons were characterized by their evoked responses and spontaneous firing patterns as described in our earlier work.[9] Neurons sampled in the region of Rexed lamina V in this study responded principally to high-threshold mechanical and to noxious thermal stimuli (skin temperature greater than 45 C), and the center of their receptive field was one of the foot pads. After control recording of the spontaneous activity of each unit for 20 min, evoked activity in each unit was obtained by radiant-heat stimulation (275 mcal/cm²/sec for 3 sec) using a Hardy-Wolff-Goodell dolorimeter

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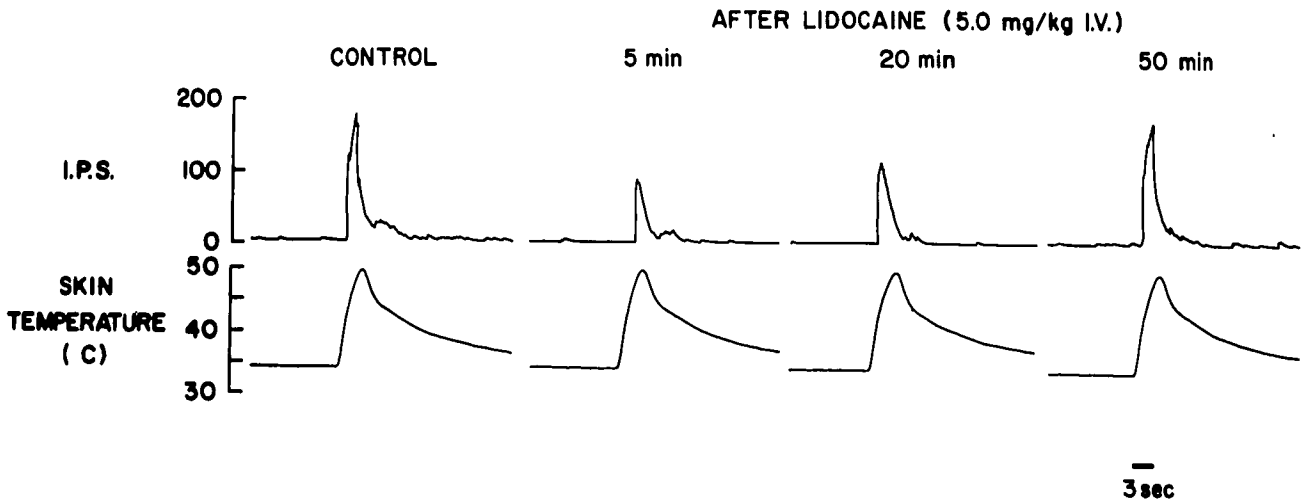

FIG. 1. Example of polygraph tracings of instantaneous firing frequencies (I.P.S. = impulses per second) of a lamina V neuron (its spontaneous activity followed by evoked activity secondary to thermal stimulation) and skin temperatures of the receptive field before and after lidocaine administration.

with a 3.5-cm^2 aperture. This stimulation was applied to the receptive field of the blackened skin and was repeated three times at 1.5–2-min intervals during a control period. Skin temperature was monitored continuously with the thermistor and recorded on magnetic tape. Thermal stimulation using the dolorimeter with 275 mcal/cm^2/sec for 3 sec increased skin temperature by 14.2 ± 0.2 degrees C (the distance between the skin and the aperture was approximately 1.5 cm). The skin temperature of the foot pad was 33–35 C before the thermal stimulation, and rose 48–50 C. Radiant-heat stimulation was such that skin temperature was kept at 51 C or less to minimize the sensitization of nociceptors[10] and possible damage to the skin.[11] The instantaneous firing frequency of single units was counted electronically, and skin temperature, arterial blood pressure and endotracheal P_{CO_2} were recorded on a polygraph.

Following the control study, lidocaine hydrochloride, either 2.5, 5 or 10 mg/kg, was administered intravenously, and both spontaneous activity and evoked single-unit activity of the neurons were observed until recovery. Plasma concentrations of lidocaine in five animals that had received lidocaine, 5 mg/kg, were measured by gas chromatography. The vital signs of the animals studied were maintained within normal ranges except in four animals in which profound arterial hypotension occurred following intravenous administration of lidocaine, 10 mg/kg. Data obtained from these animals were excluded from the study.

At the end of the experiment, electrolytic lesions were made by passing direct current through the recording microelectrode and their presence verified histologically. Data recorded on magnetic tape were processed off-line with a digital computer (DEC PDP 11/40). The control discharge frequency for spontaneous activity was averaged over 60 sec with each unit. The mean evoked discharge frequency of each unit was determined by averaging the discharge frequency observed for 17 sec immediately after each exposure of the receptive field to radiant heat. Threshold skin temperature was defined as the temperature at which the discharge frequency of a single unit increased by 20 per cent over its spontaneous activity.

Statistical significances of differences between mean values of spontaneous and evoked discharge frequencies during the control period and after administration of lidocaine were assessed by the Student *t* test; $P \leq 0.05$ defined statistical significance. Data were expressed as means ± 1 standard error.

Results

All the neurons studied responded to noxious thermal stimulation (skin temperature greater than 45 C) and progressively increased their responses with further increases in skin temperature. In addition, 15 single units of 37 neurons studied responded to pressure and to pinch, and 22 units responded to touch, pressure and pinch. The mean discharge frequency of spontaneous activity in 37 neurons was 9.5 ± 1.0 impulses/sec (ips). When radiant-heat stimuli were used, the mean value of the average discharge frequency increased to 33.9 ± 2.5 ips. The threshold skin temperature of 37 neurons studied was 44.7 ± 0.4 C.

Lidocaine administered intravenously decreased the firing frequency, both spontaneous and evoked, of lamina V dorsal-horn nociceptive neurons (fig. 1). The depressant effect of intravenously administered lidocaine on lamina V neuronal activity varied in a dose-dependent manner (fig. 2; table 1). The threshold skin temperature increased significantly from 44.7 ± 0.4 C to 46.3 ± 0.7 C and to 47.8 ± 0.8 C following

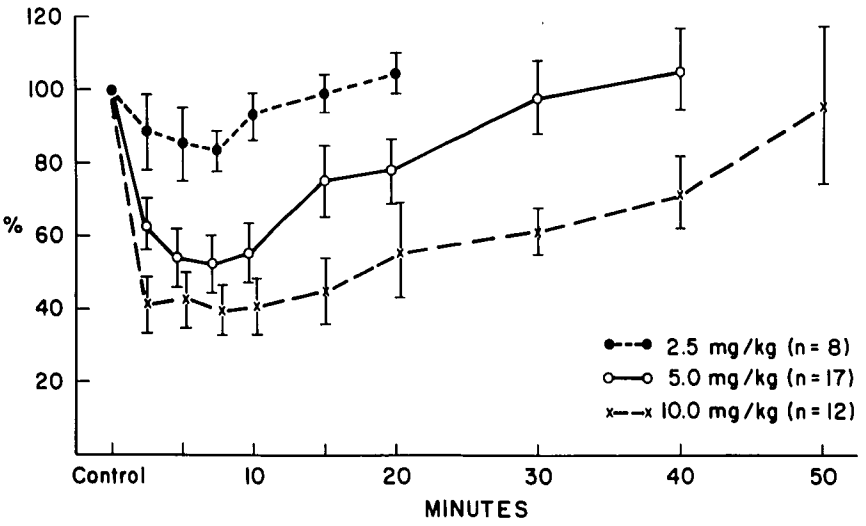

FIG. 2. Effects of intravenously administered lidocaine on Rexed lamina V single-unit activities evoked by peripheral noxious thermal stimulation, expressed as percentages (mean ± 1 SE) of control values.

lidocaine, 5 and 10 mg/kg, respectively, although it did not increase significantly following lidocaine, 2.5 mg/kg. Plasma concentrations of lidocaine in five animals 5 and 50 min after administration of lidocaine, 5 mg/kg, were 3.6 ± 0.7 and 0.7 ± 0.3 μg/ml, respectively.

Discussion

Intravenous injection of local anesthetics to treat chronic pain of arthritis and other painful illnesses enjoyed considerable popularity in the 1940s and 1950s.[12] Graubard and Peterson[13] suggested that the intravenous administration of local anesthetics provided a measure of analgesia due to conduction block in nerves or nerve terminals. It was soon found that procaine, 4 mg/kg, given intravenously over 20 min provided optimal therapeutic effects with minimal side effects; yet this quantity of procaine had little effect on conduction in peripheral nerve. Larger and therefore toxic intravenous doses of procaine (25–50 mg/kg) were necessary to depress conduction in peripheral nerve significantly.[14]

However, de Jong *et al.*[5] have shown that intravenously administered lidocaine, 5.0 to 17.5 mg/kg, depresses response amplitude and conduction time in A-delta and in C fibers in cats anesthetized with pentobarbital. C fibers are more sensitive than A-delta fibers. For example, lidocaine hydrochloride, 10 mg/kg, iv, depressed the conduction velocities of A-delta and C fibers less than 5 per cent and 10 per cent, respectively, and the amplitudes of A-delta and C fibers by 16 per cent and 27 per cent of the control values, respectively. These investigators suggested that intravenously administered lidocaine may produce analgesia by impulse-conduction block in small-diameter axons (A-delta and C fibers). Small-diameter axons are necessary for conducting impulses originating in peripheral "pain" receptors in man.[15] Noxious thermal stimulation using radiant heat activates only small myelinated (A-delta) and C fibers both in animal experiments[16] and in man.[17] Thus, in this respect, we cannot distinguish the site of action of lidocaine at the spinal level from its action at the level of the peripheral axon. However, several points suggest an action of lidocaine at the spinal level.

First, impulses in peripheral axons are propagated so long as the amplitude of the compound action potential is at least half the normal value.[18] In this respect, the suppression in amplitude of A-delta and C fibers (less than 30 per cent with lidocaine, 10 mg/kg, iv[5]) is not sufficient to block axonal impulse propagation. Wagers and Smith[6] observed that low doses (2 to 4 mg/kg, iv) of lidocaine were ineffective in decreasing the frequency of the impulses of peripheral axons evoked by constant pressure to the tooth, and a dose of 20 mg/kg was necessary to abolish compound action potentials. In the present study, the plasma lidocaine concentration that produced approximately 50 per cent suppression of evoked responses of dorsal-horn lamina V neurons was 3.6 ± 0.7 μg/ml (0.016 mM). This *in-vivo* concentration is much lower than *in-vitro*

TABLE 1. Maximum Effects of Lidocaine on Spontaneous and Evoked Single-Unit Activities of Rexed Lamina V Nociceptive Neurons*

Dose of Lidocaine	Percentage Suppression† (Mean ± SE)	
	Spontaneous	Evoked
2.5 mg/kg (n = 8)	36.5 ± 13.5	17.4 ± 5.3
5 mg/kg (n = 17)	68.1 ± 7.9	48.2 ± 8.2
10 mg/kg (n = 12)	75.0 ± 8.7	61.1 ± 7.4

* Evoked activity was produced by application of noxious thermal stimulation using a Hardy-Wolff-Goodell dolorimeter.
† $P < 0.05$ compared with control.

concentrations needed for comparable blocking of axonal conduction—0.3 mM lidocaine is necessary to block the C-fiber potential amplitude approximately 50 per cent[19] and 2.5 mM, to block compound action potentials 50–60 per cent.[20]

Second, the durations of suppression with lidocaine, 2.5, 5, and 10 mg/kg, iv, were 20, 30, and more than 50 min after injection, respectively. Wagers and Smith[6] reported that with lidocaine, 10–20 mg/kg, iv, the compound action potential of peripheral axons began to return 2 min after the injection, and recovered within 10–15 min. With regard to the recovery of amplitude of C-fiber potentials, de Jong *et al.*[5] reported that recovery began 2–3 min after the injection of lidocaine, 15 mg/kg, iv, and approximately 80 per cent recovery had occurred 10 min later. In the present study, the duration of the suppression of dorsal-horn neurons was much longer, even with lower concentrations of lidocaine (fig. 2).

Third, spinal reflexes have been shown to be depressed by intravenously administered procaine[21] and lidocaine.[7] Peterson[21] observed in cats that procaine, 4–5 mg/kg, iv, had negligible effects on axonal conduction, whereas it strongly depressed the transmission of monosynaptic and polysynaptic spinal reflexes. de Jong *et al.*[7] reported that lidocaine, 5–25 mg/kg, iv, decreased the polysynaptic response by 10–50 per cent of the control value in cats. These observations provide evidence that an action of local anesthetics, in fact, exists at a spinal level.

In the present study, effects of intravenously administered lidocaine on descending control mechanisms having their origin at supraspinal levels were ruled out by spinal-cord transection, thereby demonstrating a direct local action of the lidocaine on spinal neurons. In this regard, the effect of intravenously administered lidocaine on spinal nociceptive neurons is similar to the effects of other drugs reported in our earlier work, such as nitrous oxide,[9] morphine sulfate,[22] ketamine hydrochloride,[23] halothane, and sodium thiopental.[24] The significance of the present study is the finding that intravenously administered lidocaine produces dose-related suppression of both spontaneous and evoked discharges of dorsal-horn nociceptive neurons responding to noxious thermal stimulation, providing a partial explanation at the spinal level for analgesia produced by systemically administered local anesthetics.

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