Shimane J. Med Sci.,Vol.12, pp.23 - 30 , 1989/90

THE EFFECT OF INTRAVENOUS LIDOCAINE ON THE LESPONSE OF MEDULLARY INSPIRATORY NEURONS TO CO_2 IN CATS

(carbon dioxide / cats / lidocaine)

Toshiharu KASABA, and Yoshihiro KOSAKA

Department of Anesthesiology, Shimane Medical University, Izumo 693, Japan

(Received February 21, 1990/Accepted March 30, 1990)

The effect of intravenous lidocaine on the response of medullary inspiratory neurons to CO_2 was studied in 11 urethane-anesthetized ventilated cats. Lidocaine was administrated at a subconvulsive dose through a venous cannula by means of a constant-rate infusion pump ($0.3-0.5 mg \cdot kg^{-1} \cdot min^{-1}$). We compared the number of spikes before and after CO_2 administration in a lidocaine-free state. Then, we likewise compared the number of spikes before and after CO_2 administration in a lidocaine administered-state. The rate of increase of spikes per mmHg of $PaCO_2$ was 1.49 ± 0.72 spike$\cdot mmHg^{-1}$ in the control lidocaine-free group, and 0.96 ± 0.51 spike$\cdot mmHg^{-1}$ in the lidocaine-administered group. The response to CO_2 was significantly suppressed in the lidocaine group ($p<0.05$).

These results suggest that systemic lidocaine suppresses respiratory center in the urethane-anesthetized cats.

It has been reported that intravenous administration of lidocaine exerts a respiratory depressant action (1-3). Studies on man confirm the impression that lidocaine has a distinct sedative effect (4,5). However, a marked improvement in the ventilatory response to carbon dioxide was reported following caudal block with lidocaine (6) and intravenous and epidural lidocaine (5,7).

To obtain information on the response of the respiratory center to CO_2, the present study was designed to determine

whether lidocaine alters the number of spikes of inspiratory neurons in response to CO_2.

MATERIALS AND METHODS

Preparation

Eleven adult cats weighing 2.8-4.0kg were used. A schematic diagram is shown in Figure 1. General anesthesia was induced with halothane and maintained with urethane($1g \cdot kg^{-1}$ I.V.). After endotracheal intubation, the cats were mechanically ventilated (I:E ratio; 1:1) with a respirator(Shinano, SN-480-5). The femoral vein was cannulated for drug infusion. The femoral artery was cannulated for blood sampling and for monitoring the blood pressure. The animals were placed on a stereotaxic frame and the brain stem was exposed for microelectrode survey of neurons associated with breathing. The exposed brain stem was covered with a pool of warm paraffin oil. The chest movement was monitored pneumographically using resistance strain gages. The blood pressure was continuously monitored. Intermittent arterial blood gas analysis for PaO_2, $PaCO_2$ and pH was performed using a Radiometer ABL2 blood-gas analyser. Oxygen was added to the inspired gas to maintain PaO_2 higher than 100 mmHg.

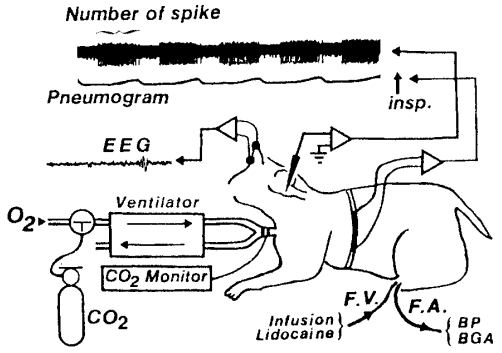

Fig.1. A schematic diagram of the recording setup. Medullary inspiratory unit was recorded with tungusten microelectrodes. The rhythmic burst discharges of respiratory neuron and pneumogram are shown at the top. EEG was recorded with surface electrodes. Femoral vein and artery were cannulated for drug administration, and monitoring the BGA and plasma lidocaine level. CO_2 was administered from the inspiratory side of respirator.

Recording

Electroencephalograms(EEG) were recorded from the frontal portion of the brain using surface electrodes fixed to the frontal skull. A reference electrode was placed in the pinna. The unit discharges of medullary inspiratory neurons were recorded extracellularly with tungusten microelectrodes. Sharply tapered tungsten electrodes(2-5 MΩ) were inserted around the nucleus ambiguus(P:14-16, L3-4). A signal from the EEG electrodes was passed through a preamplifier(Nihonkoden, S1516 0.08-30Hz) and a signal from the unit recording electrodes was passed through a

preamplifier(Nihonkoden, S1516) and then both of them were passed through respective amplifiers(Nihonkoden, AVH-10) before they were displayed on an oscilloscope(Nihonkoden, VC-9). After stable inspiratory unit recording was made, the animals were paralysed with pancuronium bromide($0.2mg \cdot kg^{-1}$). The tidal volume(20-30ml) of the respirator was controlled by the value of $PaCO_2$ to stay within a normal range($ETCO_2$ 4-5%). The vagus was left intact and their respiratory burst rhythm was synchronized with the respiratory cycle($20-30cycle \cdot min^{-1}$). We studied the response of inspiratory neurons to CO_2(2-6%). Before and after inspiration(1-2min) of CO_2 in a lidocaine free state as control, we recorded the inspiratory unit discharges and made blood sampling for determination of $PaCO_2$. Then lidocaine was administered through the venous canula by means of a constant-rate infusion pump($0.3-0.5mg \cdot kg^{-1} \cdot min^{-1}$). At 3-5minute intervals, we recorded the inspiratory unit discharges and made blood sampling for determination of the plasma lidocaine level (Clinical Systems DUPONT aca SX). CO_2(2-6%) was then added(1-2min) for the animals to inspire the gas in a lidocaine-administered state. We recorded the inspiratory unit discharges and made blood sampling for determination of $PaCO_2$. The number of spikes in each respiratory cycle was measured in each state. All the data were recorded with a photo-recorder and stored in a data-recorder(Sony, DFR-3415).

Analysis

The number of spikes per respiratory cycle was calculated in 3 successive inspiratory neuron bursts. To determine the effect of carbon dioxide, we compared the number of spikes per mmHg of $PaCO_2$ before and after lidocaine administration. The number of spikes per mmHg of $PaCO_2$ was calculated as follows: ((The number of spikes per respiratory cycle after CO_2 was added to inspire the gas) - (The number of spikes per respiratory cycle before CO_2 was added to inspire the gas))/(($PaCO_2$ value after CO_2 was added to inspire the gas) - ($PaCO_2$ value before CO_2 was added to inspire the gas)). When the number of spikes per mmHg of $PaCO_2$ in one neuron was record at more than three points, the value was calculated by the method of least squares. And the data before and after lidocaine administration were analyzed using student's unpaired t-test. $P<0.05$ was considered significant. All the results are expressed as mean $\pm$ SD.

RESULTS AND DISCUSSION

The numbers of spikes of inspiratory neuron in response to CO_2 are shown in Table I, Table II. The rate of increase of spike frequency per mmHg of $PaCO_2$ was 1.49 ± 0.72 spike·mmHg^{-1} in the control lidocaine-free group, and 0.96 ± 0.51 spike·mmHg^{-1} in the lidocaine-administered group. The difference in the rate of increase of spike frequency was significant ($P < 0.05$).

Table I. EFFECT OF CO2 ON THE INSPIRATORY UNIT BEFORE LIDOCAINE ADMINISTRATION

Unit	PaCO2	Spike	Spike·mmHg^{-1}
3	47.8	22	0.67
	65.7	34	
5	35.6	94	1.39
	69.7	140	
6	44.5	17	1.80
	50.5	22	
	60.6	45	
15	43.2	16	2.86
	51.6	40	
16	43.1	43	1.10
	88.6	93	
19	32.7	18	1.76
	54.3	56	
20	46.9	52	2.12
	51.0	60	
	60.2	80	
21-1	38.2	16	0.67
	43.9	22	
	50.8	29	
	60.6	34	
	69.1	37	
21-2	42.3	15	1.0
	50.3	23	
			1.49±0.72*

Two units were recorded simultaneously in 21 units.
Spike = the number of spikes per respiration
Spike·mmHg^{-1} = the number of spikes per mmHg of CO2
* Values are mean ± SD

The present study showed that the rate of increase of the inspiratory unit discharge to CO_2 per mmHg decreased significantly by intravenous lidocaine. This means that intravenous lidocaine suppresses inspiratory neuron in the urethane-anesthetized cats. These results are coincident with the

clinical reports that intravenous administration of lidocaine exerts a respiratory depressant action (1-3). However, a marked improvement in the ventilatory response to CO_2 was also reported following caudal block with lidocaine (6) and intravenous and epidural lidocaine (5,7). Our suppressive effect of intravenous lidocaine on the inspiratory neuron was different from the increased ventilatory responsiveness regarding response to CO_2. We considered the difference on the following three points.

Table II . EFFECT OF CO2 ON THE INSPIRATORY UNIT AFTER LIDOCAINE ADMINISTRATION

Unit	PaCO2	Spike	Spike·mmHg^{-1}
5	30.6	70	1.03
(8.0)	50.2	91	
	64.6	105	
5	33.3	80	0.58
(9.0)	56.3	90	
	76.4	105	
5	32.4	76	0.57
(10.0)	58.3	88	
	73.4	100	
9	46.4	8	0.71
(3.8)	49.2	17	
	77.7	35	
	89.7	41	
11	41.3	71	0.44
(6.6)	54.8	90	
	63.8	90	
	77.4	88	
17	38.6	37	2.50
(8.1)	46.7	57	
19-1	36.0	44	1.05
(2.9)	51.3	61	
	68.4	78	
19-1	45.5	56	0.85
(3.8)	54.6	62	
	69.4	76	
19-1	41.6	71	1.31
(4.9)	67.5	105	
19-2	36.0	9	0.80
(2.9)	51.3	22	
	68.4	35	
19-2	45.5	12	0.59
(3.8)	54.6	16	
	69.4	26	
19-2	41.6	57	0.54
(4.9)	67.5	71	
20	48.6	62	1.22
(0.6)	63.3	80	
20	44.4	52	1.20
(3.4)	61.1	72	
20	50.3	70	0.94
(5.0)	80.0	98	
			0.96±0.51*

Continued from right to left. Figures in parentheses indicate lidocaine plasma level ($\mu g \cdot ml^{-1}$). Two units were recorded simultaneously in 19 units.
Spike = the number of spikes per respiration
Spike·mmHg^{-1} = the number of spikes per mmHg of CO2
* Values are mean ± SD

1) Plasma lidocaine concentration.

Gross et al. (7) demonstrated that an intravenous bolus administration of lidocaine caused significant but transient depression of the ventilatory response to hypercarbia, while therapeutic steady-state lidocaine concentrations increased the response to hypercarbia in healthy, unmedicated volunteers.

Nishino et al (8) showed that the phrenic nerve activity was depressed by rapid injection of 2mg·kg^{-1} of lidocaine in -chloralose anesthetized cats. They noted that a subconvulsive dose of lidocaine can evoke an excitatory activity in various areas of the brain. These mean that high plasma lidocaine concentration suppresses the ventilation, while lower concentration activates it.

Tanaka et al. (9) reported that the inhibitory synapses of cortical neurons are selectively blocked by lidocaine administrated intravenously and the excitatory synapses are more resistant to the drug. Local anesthetics probably lead initially to depression of cortical inhibitory pathways thereby allowing an unopposed activity of excitatory nature.

Seo et al. (10) showed that lidocaine had a multiphasic dose-dependent action on the CNS of cats. Early EEG manifestations included an initial period of reticular depression followed by a stage of reticular and amygdaloid excitation. It is conceivable that this stage of excitation is the counterpart of the increased CO_2 sensitivity. They showed that the plasma level of lidocaine was 10.3 $\pm$ 0.6u·g ml^{-1} during excitation phase in the cats. In our experiment the plasma level of lidocaine increased up to 10.0 μ·g ml^{-1}. Our results of lidocaine concentrations were similar to the report of Seo et al. during excitation phase in the cats. In this experiments we did not comfirm the inspiratory neuron as interneuron or output neuron to connect to phrenic motoneuron (11). The influence on the CNS in lidocaine-administrated animal might not be direct cause to the increase in the number of spikes of inspiratory neurons. Labaille et al. (5) reported that an increasing plasma lidocaine or bupivacaine level steepened the slope of the response curve. However, our lidocaine study demonstrated no correlation between the plasma lidocaine level and the changes in the number of spikes of the inspiratory neuron nor its increase in the response to CO_2 .

2) Other anesthetics influence to the response to CO_2.

Patients without impairment of the ventilatory response to CO_2 are anesthetized with enflurane (3), ether (1) or halothane (2). Many volatile anesthetics have been known to decrease the slope of ventilatory response to CO_2 (12). Volatile anesthetics probably suppress both inhibitory and excitatory pathways. The ventilatory depressant effect of lidocaine may be masked by other

volatile CNS depressant. The improvement in the ventilatory response to CO_2 was reported unmedicated volunteers (5,7) sedated children (6). The animals in this study were lightly anesthetized with urethane. Though we compare the response to CO_2 in this same basic condition, urethane anesthesia might suppress and change the response to CO_2.

3) Artifitial and spontaneous ventilation.

The response to CO_2 was usually measured at the condition of spontaneous ventilation. In our experiment, we measured the changes in the number of spikes of inspiratory neuron to CO_2. The animals were paralyzed and ventilated artificially. The difference in methodology, the ventilatory response to CO_2 by spontaneous ventilation or the changes in the number of spikes by artificial ventilation might alter the CO_2 response. We compared the number of spikes in the burst of inspiratory neurons which were synchronized with the artificial ventilation. In our previous observation (13), artificial ventilation suppress the phrenic nerve activities. These mean suppress the inspiratory center, and might change the response to CO_2 before and after lidocaine-administration. Only spontaneous ventilation might change the respiratory movement and might produce the increase in the response to CO_2. To clear this artificial afferent effects, we need further study on the response to CO_2 in vagotomyzed cats.

Though the reasons of the improvement of ventilatory response following caudal block and intravenous and epidural lidocaine are unclear, some specific conditions such as unmedicated volunteers ventilated spontaneously and subconvulsive lidocaine level might increase the response the CO_2. Considering our usual anesthetized condition, general anesthesia with volatile anesthetics and epidural block with lidocaine and ventilated artificially, we need to take notice of the respiratory depression in these patients.

This study was supported in part by Grants-in-Aid (No. 63771145) for Scientific Research from The Ministry of Education, Science and Culture of Japan.

REFERENCES

1) Siebecker K.L., Kimmey J.R., Bamforth B.J., and Steinhaus

J.E. (1960) Effect of lidocaine administrated intravenously during ether anesthesia. Acta Anaesthesiol. Scand., 4, 97-103

2) Telivuo L., and Katz R. (1970) The effects of modern intravenous local analgesics on respiration during partial neuromuscular block in man. Anaesthesia, 25, 30-35

3) Himes R.S., Munson E.S., and Embro W.J. (1979) Enflurane requirement and ventilatory response to carbon dioxide during lidocaine infusion in dog. Anesthesiology, 51, 131-134

4) Wagman I.H., deJong R.H., and Prince D.A. (1967) Effects of lidocaine on the central nervous system. Anesthesiology, 28, 155-172

5) Labaille T., Clergue F., Samii K., Ecoffey C., and Berdeaux A. (1985) Ventilatory response to CO_2 following intravenous and epidural lidocaine. Anesthesiology, 63, 179-183

6) Takasaki M. (1988) Ventilation and ventilatory response to carbon dioxide during caudal anaesthesia with lidocaine or bupivacaine in sedated children. Acta Anaesthesiol. Scand., 32, 218-221

7) Gross J.B., Caldwell C.B., Shaw L.M., and Laucks S.O. (1983) The effect of lidocaine on the ventilatory responses to carbon dioxide. Anesthesiology, 59, 521-525

8) Nishino T., Yonezawa T., and Honda Y. (1982) Different laryngeal responses during respiratory arrest produced by hypoxia withdrawal, thiopentone, ketamine, and lidocaine in cats. Anesthesiology, 56, 280-285

9) Tanaka K., and Yamasaki M. (1966) Blocking of cortical inhibitory synapses by intravenous lidocaine. Nature, 209, 207-208

10) Seo N., Oshima E., Stevens J., and Mori K. (1982) The tetraphasic action of lidocaine of CNS electrical activity and behavior in cats. Anesthesiology, 57, 451-457

11) Merrill E.G. (1970) The lateral respiratory neurones of the medulla; Their associations with nucleus ambiguus, nucleus retroambigualis, the spinal accessory nucleus and the spinal cord. Brain Research, 24, 11-28

12) Stoelting R.K. (1987) In: Pharmacology and physiology in anesthetic practice, pp.50-52, J B Lippincott Co., Philadelphia

13) Kasaba T., and Kosaka Y. (1988) Phrenic nerve and vagal nerve activities during differential lung ventilation in cats. J. Anesth., 2, 170-175