Timing of Injection and Plasma Concentration of Lidocaine before Endotracheal Intubation

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The optimal time of intravenous lidocaine for attenuation of pressor responses to laryngoscopy and endotracheal intubation was evaluated in fifty adult patients and the correlation between plasma lidocaine level and its clinical effects were also studied.

The plasma lidocaine levels were highest 0.5 min after administration of lidocaine 1.5 $mg \cdot kg^{-1}$ intravenously. However, endotracheal intubation 0.5 min after lidocaine administration caused significant increase in mean arterial pressure (MAP) and heart rate (HR). Mean arterial pressure and HR increased with endotracheal intubation following 1, 2 and 3 min after lidocaine administration, but the magnitude of increase was not statistically significant. There were no significant differences in MAP changes among these three groups. It was concluded that the plasma lidocaine levels did not correlate with its suppressive effect on circulatory responses due to laryngoscopy and endotracheal intubation. Laryngoscopy and endotracheal intubation should be carried out at least 1 min after intravenous lidocaine administration. (Key words: Lidocaine, Laryngoscopy, Endotracheal intubation, Plasma concentration)

(Okuda M, Ohi Y, Kurata M et al.: Timing of injection and plasma concentration of lidocaine before endotracheal intubation. J Anesth 4: 150–154, 1990)

Laryngoscopy and endotracheal intubation cause hypertension and tachycardia[1,2]. Intravenous lidocaine administration before endotracheal intubation is a popular method used to attenuate these harmful responses[3–5]. Abou-Madi et al.[4] demonstrated that a large dose of lidocaine was more effective in attenuating circulatory responses to endotracheal intubation. Therefore, the plasma level of lidocaine may be one factor involved in attenuating these responses, as well as the timing of lidocaine injection. Tam et al.[5] reported that the optimal time of injection was 3 min before intubation. However, the blood level of lidocaine was not taken into consideration in Tam's study.

The purpose of this study is to evaluate the correlation between blood level of lidocaine and its attenuating effect to circulatory responses accompanied by laryngoscopy and tracheal intubation as well as the optimal time of injection of IV lidocaine.

Patients and Methods

Fifty adult patients without known history of hypertension and ischemic heart disease, scheduled for elective noncardiac surgery were studied. The informed consent was taken from the patients and the study was approved by the ethic committee of hospital. These patients were randomly divided into five groups of 10 patients each. Group I patients served as controls and received no li-

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Table 1. Characteristics of patient population

Group	n	age (yr)	weight (kg)	height (cm)
I	10	44 ± 14	53 ± 9	156 ± 6
II	10	51 ± 15	55 ± 12	159 ± 9
III	10	54 ± 12	54 ± 10	158 ± 5
IV	10	51 ± 17	58 ± 13	160 ± 10
V	10	48 ± 8	57 ± 9	164 ± 6
		NS	NS	NS

NS, not significant. (mean ± SD)

docaine. Patients in groups II, III, IV and V received lidocaine intravenously 1.5 $mg \cdot kg^{-1}$ 0.5, 1, 2 and 3 min before laryngoscopy and endotracheal intubation, respectively. Lidocaine was injected intravenously as a single bolus within 15-seconds. Preanesthetic medication consisted of IM administration of diazepam 10 mg and atropine sulfate 0.5 mg 1 hr before induction of anesthesia. In the operating room, a radial artery was cannulated for arterial pressure monitoring and blood sampling. Cardiac rhythm and heart rate (HR) were monitored by a continuous recording of the ECG.

Anesthesia was induced by thiopental (4 $mg \cdot kg^{-1}$), fentanyl (5 $\mu g \cdot kg^{-1}$) and vecuronium (0.2 $mg \cdot kg^{-1}$) IV 3 min before intubation and the patients were ventilated with oxygen-nitrous oxide (3L:3L).

Heart rate and mean arterial pressure (MAP) were recorded before induction of anesthesia, just before laryngoscopy and endotracheal intubation, and 0.5, 1, 3 and 5 min after starting laryngoscopy and endotracheal intubation. Arterial blood samples were drawn before injection of lidocaine, at endotracheal intubation, 1, 3 and 5 min after endotracheal intubation in groups II, III, IV and V. Plasma lidocaine concentration was

Table 2. Hemodynamic data and changes in plasma lidocaine concentration

		pre-intubation	after starting laryngoscopy and intubation			
	awake	0 min	0.5 min	1 min	3 min	5 min
Group I						
MAP (mmHg)	90 ± 12	88 ± 16	113 ± 20*#	108 ± 20*#	99 ± 14*	91 ± 12
HR (bpm)	71 ± 8	73 ± 15	96 ± 17*#	86 ± 21	77 ± 17	73 ± 15
Group II						
MAP (mmHg)	91 ± 14	79 ± 15	97 ± 25*	85 ± 23	77 ± 17	71 ± 12
HR (bpm)	69 ± 11	73 ± 17	88 ± 25*#	86 ± 28*	77 ± 19	70 ± 17
Lidocaine ($\mu g \cdot ml^{-1}$)	0.03 ± 0.01	11.72 ± 3.20#		5.29 ± 1.97#	2.45 ± 0.57#	1.96 ± 0.36#
Group III						
MAP (mmHg)	94 ± 8	85 ± 16	92 ± 15	98 ± 22	90 ± 14	85 ± 10#
HR (bpm)	71 ± 8	83 ± 18	84 ± 15	86 ± 16	82 ± 13	80 ± 11
Lidocaine ($\mu g \cdot ml^{-1}$)	0.02 ± 0.02	9.08 ± 3.28#		5.60 ± 4.10#	2.29 ± 1.02#	1.67 ± 0.71#
Group IV						
MAP (mmHg)	93 ± 12	87 ± 13	95 ± 18	98 ± 22	90 ± 14	85 ± 10
HR (bpm)	78 ± 11	85 ± 16	86 ± 17	86 ± 16,	82 ± 13	80 ± 11
Lidocaine ($\mu g \cdot ml^{-1}$)	0.02 ± 0.02	1.44 ± 0.42#		1.13 ± 0.59#	0.71 ± 0.46#	0.51 ± 0.37#
Group V						
MAP (mmHg)	93 ± 9*	85 ± 11#	92 ± 16	92 ± 14	87 ± 13#	84 ± 14#
HR (bpm)	76 ± 13	80 ± 17	84 ± 16	83 ± 19	78 ± 20	74 ± 20
Lidocaine ($\mu g \cdot ml^{-1}$)	0.02 ± 0.01	0.86 ± 0.47#		0.64 ± 0.50#	0.47 ± 0.34#	0.36 ± 0.31#

(mean ± SD)

#$P < 0.05$ compared with awake value. *$P < 0.05$ compared with pre-intubation value.

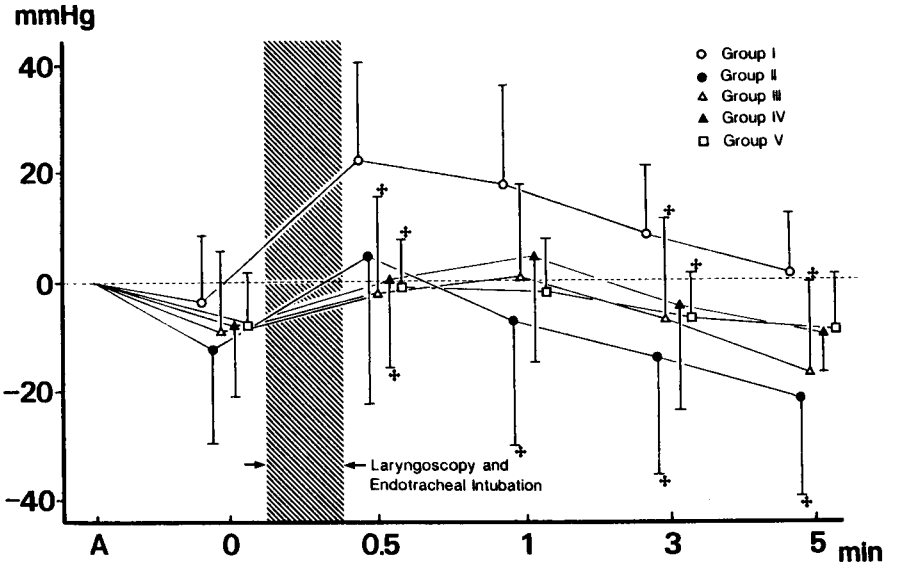

Fig. 1. Changes in mean arterial pressure (MAP) as compared to awake value (mean ± SD).
A, At arrival of the patients in the operating room.
✣: $P < 0.05$ compared with group I.

measured using a fluorescence polarization immunoassay (TDX analyzer. Abott Laboratories).

Results are presented as mean ± SD. Data were analyzed using Students' t-test and $P < 0.05$ considered significant.

Results

There were no differences in age distribution, body weight and height among the five groups of patients (table 1). Results are shown in table 2. In all patients, laryngoscopy and endotracheal intubation were carried out within 30 seconds. In all groups, MAP decreased after induction of anesthesia but not significantly, except for group V. Following the endotracheal intubation, groups I and II showed a significant increase in MAP compared with pre-intubation levels. In lidocaine administration groups, the increase in MAP returned to the pre-intubation values more quickly than that in the control group. The significant increase in MAP persisted for 3 min in group I. Figure 1 shows the changes in MAP from awake levels. 0.5 min after starting laryngoscopy and endotracheal intubation, changes in MAP of group I were greater than those in groups III, IV and V ($P < 0.05$). MAP showed minimal change in groups III, IV and V. Heart rate increased significantly in group I at 0.5 min and in group II at 0.5 and 1 min (table 2). There were no significant differences in HR between awake state and after endotracheal intubation among the five groups.

Plasma lidocaine levels of each group were shown in table 2. The highest level at laryngoscopy and endotracheal intubation was found in group II. The lowest level at laryngoscopy and endotracheal intubation was found in group V.

Discussion

Intravenous lidocaine can attenuate the circulatory responses due to laryngoscopy and endotracheal intubation. The factors probably involved in these effects are lidocaine dose, the time of injection of lidocaine and duration of laryngoscopy[4–6]. The dose of intravenous lidocaine for attenuation of circulatory responses to laryngoscopy and endotracheal intubation have

been recommended at 1.5 mg·kg^{-1}.[4] Tam et al.[5] reported that IV lidocaine at a dose of 1.5 mg·kg^{-1} attenuated increases in HR and MAP when given 3 min prior to laryngoscopy and endotracheal intubation. Stoelting[6] demonstrated that attempts to attenuate pressor responses due to laryngoscopy and endotracheal intubation would be appropriate when intubation procedure is likely to take more than 30 seconds. In the present study, laryngoscopy and endotracheal intubation was completed within 30 seconds in all cases. The mechanism by which intravenous lidocaine attenuates the circulatory responses is still unclear but proposed mechanisms consisted of a direct myocardial depressant and vasodilating effect[7], a central stimulant effect[8] and an effect on sympathetic transmission[9]. The plasma level of lidocaine for direct cardiac depressant and peripheral vasodilating effects has been accepted to be 1.5–5.5 μg·ml^{-1} [7]. Toxicity for the central nervous system may be seen when plasma lidocaine levels are 5–6 μg·ml^{-1} in conscious subjects[10], and 10 μg·ml^{-1} in anesthetized patients[11]. In groups II and III, plasma lidocaine levels during laryngoscopy and endotracheal intubation were 11.7 and 9.1 μg·ml^{-1}, respectively. However, among the groups administered lidocaine, the changes in MAP and HR just after the laryngoscopy and endotracheal intubation were greatest in group II. These findings indicate that the plasma lidocaine concentration dose not correlate with the attenuation of circulatory response to laryngoscopy and endotracheal intubation. Therefore, it was considered that the tissue level rather than blood level of lidocaine might be important to attenuate the circulatory responses. Benowitz et al.[12] demonstrated that the distribution of lidocaine to the brain and rapidly equilibrating tissues peaked within several minutes after one minute injection of 100 mg in a 70 kg human subject. Lidocaine levels of neural tissue and myocardium may still be low at 0.5 min after lidocaine administration. We assume that the clinical effects of lidocaine correlate with the tissue concentration of lidocaine, which will be reached the effective level several minutes after IV indocaine administration. Group II showed a significant increase in MAP following laryngoscopy and endotracheal intubation but with a more rapid return of MAP to pre-intubation levels than group I, III, IV and V. These results indicate that the tissue lidocaine concentrations reached the effective level to attenuate the pressor responses after laryngoscopy and endotracheal intubation in group II.

In the present study, changes in MAP and HR were attenuated most effectively when lidocaine was given more than 1 min before intubation. Tam et al.[5] reported that IV lidocaine at 1.5 mg·kg^{-1} attenuated increases in MAP and HR effectively when given 3 min before intubation. For induction of anesthesia they used d-tubocurarine, thiopental and succinylcholine, whereas we used fentanyl, vecuronium and thiopental under inhalation of nitrous oxide in oxygen. Therefore, it is considered that the different results obtained in this study concerning the optimal time for IV lidocaine are due to the differences in depth of general anesthesia.

Finally, the peak levels in Grouop II and III exceeded CNS toxicity levels. In the groups IV and V, the CNS toxicity level may have been reached within 30 seconds after lidocaine 1.5 mg·kg^{-1} IV bolus. In the present study, we did not detect any signs of CNS toxicity, and all patients recovered uneventfully. However, the possibility of CNS toxity due to lidocaine should not be neglected.

We conclude that lidocaine should be administered at least 1 min before laryngoscopy and endotracheal intubation with fentanyl-nitrous oxide anesthesia. It was indicated that the clinical effects of attenuation of circulatory responses to laryngoscopy and endotracheal intubation did not correlate with plasma lidocaine concentrations. In addition, it should not be neglected that the peak plasma concentration of lidocaine may reach more than 10 μg·ml^{-1} after 1.5 mg·kg^{-1} IV bolus.

Acknowledgment: The authors are thankful to Mr. T. Takeuchi, Dainabot LTD. Co. for the lidocaine concentration assays.

(Received Jul. 24, 1989, accepted for publication Oct. 23, 1989)

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