New Lidocaine Ester Derivatives with a Prolonged Anesthetic Effect

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In order to find a new long acting local anesthetic, methyl, ethyl, and butyl ester derivatives of lidocaine were synthesized in our laboratory. The topical anesthetic activity was studied with the effects on corneal reflex in rabbits, and the duration of action with those on the action potential of rabbit vagus nerve was studied in vitro. All drugs showed adequate topical anesthetic activities. The onset time to induce a complete blockage of the action potential in the excised vagus nerve was 97.1 ± 6.3 s for lidocaine, 289.3 ± 29.0 s for methyl ester, 186.3 ± 18.4 s for ethyl ester, and 85.3 ± 9.0 s for butyl ester. The mean duration of action, which was assessed as the time to recover from the complete block to 30% of control amplitude in a drug-free medium, was 32.5 ± 3.1 min for lidocaine, 39.9 ± 11.3 min for methyl ester, 68.2 ± 4.2 min for ethyl ester, and 108.7 ± 12.3 min for butyl ester. The differences in the duration of action between the ester derivatives and the original lidocaine were all statistically significant. The duration of action of all drugs studied paralleled with their protein binding capacities. These findings indicate the possibility that the ester derivatives studied, especially butyl ester, can be used as a long acting local anesthetic. (Key words: new local anesthetics, lidocaine ester derivatives, long acting agents, synthesis, high lipid solubility.)

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Emphasis has recently been placed on the development of local anesthetics with longer duration of action[1–3]. The effect of both bupivacaine and etidocaine, for example, is significantly longer than that of lidocaine[1], but they are both more toxic[4–6], and so not ideal. The present study attempted to develop a new local anesthetic with longer duration of action than lidocaine. Methyl (Li-Me), ethyl (Li-Et) and butyl ester (Li-Bu) derivatives of lidocaine were synthesized and their duration of action were compared with lidocaine.

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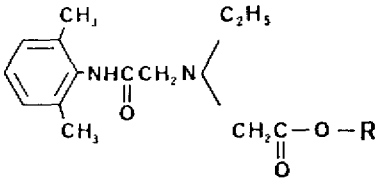
Materials and Methods

Preparation of lidocaine ester derivatives

Following a method previously used[7], a mixture of lidocaine carboxylic acid and a corresponding absolute alcohol, i.e., methyl, ethyl, or butyl, was saturated with dry hydrogen chloride gas and refluxed for 2 hr. The lidocaine ester hydrochlorides were then crystallized by cooling (fig. 1). The melting points (mp) of these ester derivatives were 170 ~ 172°C for Li-Me, 159 ~ 162°C for Li-Et, and 121 ~ 123°C for Li-Bu. All compounds showed acceptable analytical and spectral data (the IR, Mass, the ^{1}H-NMR and ^{13}C-NMR). The physicochemical proper-



R=CH_3 (Methyl ester)
R=C_2H_5 (Ethyl ester)
R=$(CH_2)_3CH_3$ (Butyl ester)

Fig. 1. Structure of lidocaine ester derivatives.

The melting point ranges are 170 ~ 172°C for methyl ester (Li-Me), 159 ~ 162°C for ethyl ester (Li-Et), and 121 ~ 123°C for butyl ester (Li-Bu).

ties (pKa, partition coefficient[8], and protein bindings[9]) and chemical structures are shown in table 1.

Experiment I

The topical anesthetic effect of each agent was tested on 30 adult New Zealand white rabbit. One drop of 100 mM solution of the ester derivatives dissolved in distilled water was applied to the corneas, and the length of absence of corneal reflex was determined every two minutes by stimulation with a 0.23 mm diameter wire. The topical anesthetic effects of the 3 derivatives were then compared with the effect of 100 mM of lidocaine.

Experiment II

Forty five adult, New Zealand, white rabbits were sacrificed by air embolus, and within 5 min the appriximately 40 mm long vagus nerve was excised. The nerves were temporarily stored at room temperature in modified Liley solution aerated with 95% O_2 and 5% CO_2. The modified Liley solution consisted of 136.8 mM of NaCl, 5.0 mM of KCl, 2.0 mM of $CaCl_2$, 1.0 mM of MgCl, 11.0 mM of dextrose, and Hepes buffer [4-(2 hydroxyethyl)-1-piperazine-ethane sulfonic acid]. The pH was adjusted to 7.4 with 0.1N NaOH[10].

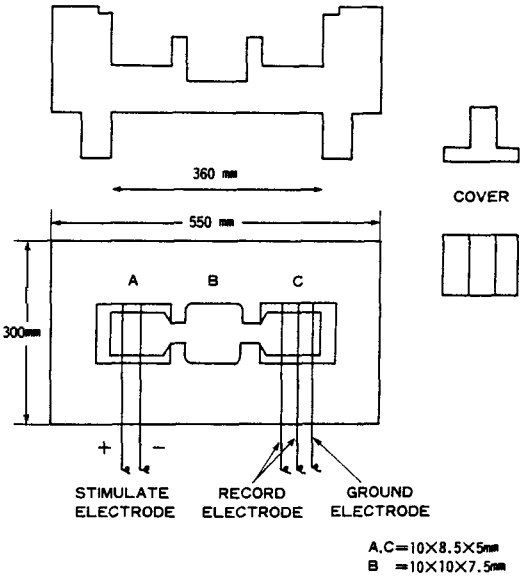


Fig. 2. Layout of the plastic chamber.

Stimulating and recording electrodes were bare platinum wire 0.3 mm diameter. Dimensions as indicated above. The groove between the wells was 3 mm long and was filled with vasaline after the vagus nerve had been positioned horizontally to stretch from well A to well C.

The nerve chamber was made of plastic and was composed of three connecting wells (fig. 2). The stimulating and recording electrodes consisted of a couple of bare pla-

Table 1. Physicochemical properties of lidocaine and lidocaine ester derivatives

	pKa (20°C)	Partition coefficient	'Protein binding (%)
Lidocaine	7.9	0.18	52
Lidocaine-methyl ester (Li-Me)	7.8	0.03	47
Lidocaine-ethyl ester (Li-Et)	7.7	0.15	60
Lidocaine-butyl ester (Li-Bu)	7.5	1.13	89

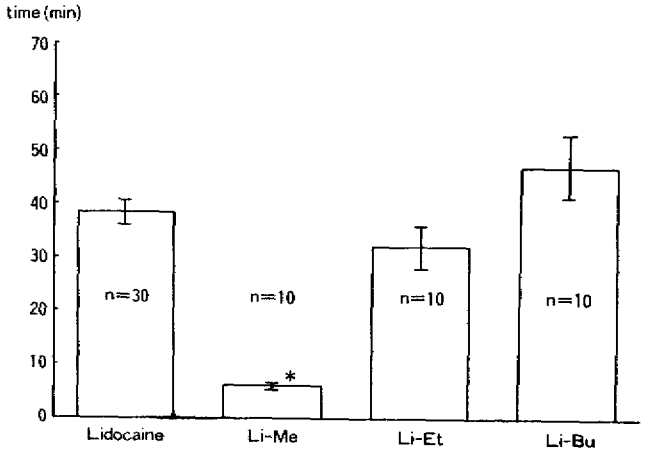


Fig. 3. Mean ± SE duration time (min) of the topical anesthetic effect of lidocaine and lidocaine ester derivatives on the corneal reflex of the rabbit ($*P < 0.01$ in the ANOVA and Duncan' test)

tinium wires separated 3 mm apart. The two end wells, one used for stimulating and the other for recording, were both 10 mm long, 8.5 mm wide, and 5 mm deep. The central well, used for the drug application, was 10 mm long, 10 mm wide, 7.5 mm deep. The three wells were interconnected with a short 3.5 mm long groove. After the vagus nerve was placed in the chamber, the wells were isolated with vaseline placed in the grooves, and made airtight with a plastic cover. During the control period, the central well was filled with Liley solution. Then, the wells were drained and filled with a 1% solution of each of the tested drugs until the action potential (AP) completely disappeared (onset), after which the test drug solution was replaced with Liley solution.

The APs were measured with a computer-programmed averager, the NEURO PACK II plus system (NIHON KOHDEN). Rectangular pulses of 10 msec duration and 14 V intensity were used. The responses of a 100 ms post-stimulus period was averaged for 32 stimuli. The duration of the drug action was defined as the time required to recover from the complete block to 30% of the control AP amplitude.

The analysis of variance were evaluated by a one-way ANOVA and Duncan's new multiplerange test, and the value less than 0.05 were considered statistically significant.

Results

Corneal reflex study

The topical anesthetic effect of lidocaine and the three lidocaine derivatives was comfirmed (fig. 3). Duration of action was 38.5 ± 2.2 min (mean ± SE) for lidocaine, 6.2 ± 1.0 min for Li-Me, 32.2 ± 4.2 for Li-Et, and 47.2 ± 6.8 min for Li-Bu. The action of Li-Me was significantly shorter than that of lidocaine, and the differences between lidocaine, Li-Et, and Li-Bu were not significant.

Vagus nerve study

The onset was 97.1 ± 6.3 s (mean ± SE) for lidocaine, 289.3 ± 29.0 s for Li-Me, 186.3 ± 18.4 s for Li-Et, and 85.3 ± 9.0 s for Li-Bu (fig. 4). The onset of Li-Me and Li-Et were both statistically slower than that of lidocaine.

The duration of the conduction blockade was 32.5 ± 3.1 min (mean ± SE) for lidocaine, 39.9 ± 11.3 min for Li-Me, 68.2 ± 4.2 min for Li-Et, and 108.7 ± 12.3 min for Li-Bu (fig. 5). The duration of the conduction blokage for all ester derivatives were statistically longer than that of lidocaine.

Discussion

The present study indicated that the ester derivatives of lidocaine had different durations of action from that of lidocaine. The topical action of methyl ester derivative was shorter, but ethyl and butyl esters were similar to lidocaine. The duration of action of

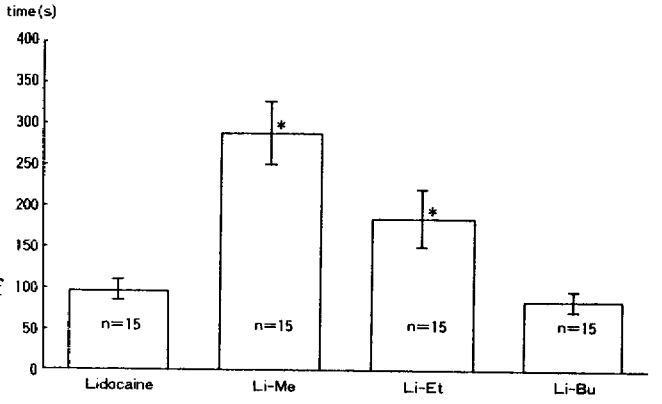


Fig. 4. Mean ± SE onset time (s) of the conduction blockade of the lidocaine and the lidocaine ester derivatives on the excised rabbit vagus nerve ($^*P < 0.05$).

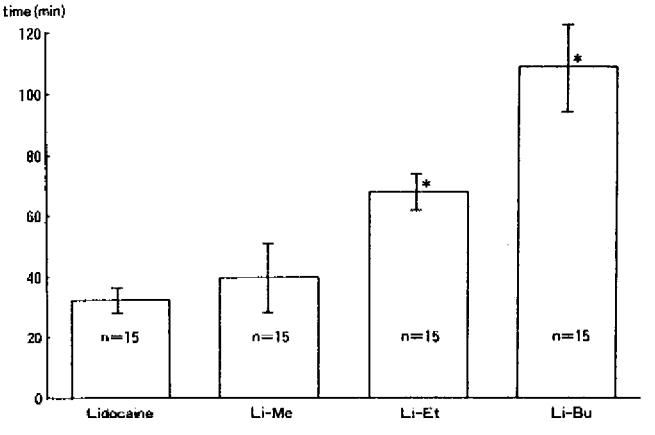


Fig. 5. Mean ± SE duration (min) of the conduction blockade of the lidocaine and lidocaine ester derivatives on the excised rabbit vagus nerve ($^*P < 0.001$).

methyl ester on excised rabbit vagus nerve was similar, but with ethyl and butyl ester derivatives it was longer than lidocaine.

The basis of differences in the duration of action on the topical and the direct nerve application in not available. The lacrimation and wiping action of cornea with a nictitating membrane does not satisfactorily explain these differences. It must be a result of mixture of differences in the lipid and water solubilities, the protein binding capacities, pKa, and others. Nevertheless, the duration of action on the vagus nerve indicates a longer duration of action when they are used for nerve blocking in clinical situations.

The site of action of local anesthetics is on the sodium channel of the nerve membrane, which consistes of protein, and the duration of action is influenced by the affinity to protein[11,12]. Wildsmith et al.[13] showed a faster washout of local anesthetics such as procaine which is bound poorly to protein while bupivacaine and other drugs, which bind firmly to protein, dissipate at extremely slower rates. The protein binding capacity of drugs studied in the present study showed the greatest protein binding of butyl ester and the smallest binding of lidocaine, which explains the significantly prolonged action of butyl ester.

Buchi and Perica[14] postulated three types of drug-receptor binding: van der Wall' forces, the dipole-dipole interaction, and electrostatic binding. The lidocaine ester derivatives studied have two carbonyl oxygen atoms, which bind to the receptor with electrostatic interaction. This may also partly explain the longer duration of action of the ester derivatives in the present study.

The onset of action of local anesthetics

is determined by the speed of diffusion in the tissue and penetration of the lipid membrane, which are achieved by a non-ionized base form. The smaller the pKa, the greater portion of the drug exist in non-ionized form, and butyl ester which has a smaller pKa showed the fastest onset.

The termination of local anesthetic action is determined by absorption of the drug from the site of application. The penetration of drug through the lipid layer of the capillary membrane is thus greater when the lipid solubility is greater. Of the three lidocaine derivatives and lidocaine, butyl ester had the greatest lipid solubility and the longest duration of action in the present study.

The CNS toxicity of local anesthetics is proportional to the potency of local anesthetic activity. Since the potency of local anesthetic activity was not studied on a mM concentration basis, the relationship between CNS toxicity and the duration of action can not be discussed in the present study.

In conclusion, the ester derivatives of lidocaine, especially butyl ester, had the longest duration of action when applied to the excised vagus nerve. When the potency and the toxicity of local anesthetic action are determined, this derivative may be used as a long acting local anesthetics in clinical applications.

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