It has been established that lignocaine and other local anaesthetic agents block neuromuscular transmission at relatively low concentrations in animals (Usubiaga and Standaert, 1968; Galindo, 1971; Blaber, 1973; Ehrenpreis and Rosen, 1974) and in man (Usubiaga and Moya, 1968; Katz and Gissen, 1969).

Straughan (1961), Usubiaga and Standaert (1968) and Blaber (1973) pointed out that the tissue most sensitive to these local anaesthetic agents is the motor nerve terminal, and Katz and Gissen (1969) reported that the neuromuscular block produced by local anaesthetic agents differs from that produced by tubocurarine because edrophonium does not antagonize the block consistently. During partial neuromuscular block produced by muscle relaxants in man, it has been demonstrated by the authors (Suzuki et al., 1975) that two characteristic responses in the recovery curves of muscle action potentials evoked by indirect stimulation are induced in accordance with the mode of action of the relaxants, whether competitive or depolarizing.

The purpose of this investigation was to determine the type of recovery curve of muscle action potential with lignocaine, and to compare it with that of muscle relaxants.

**METHODS**

Ten healthy adult patients of both sexes, aged 20–50 yr, undergoing minor surgical procedures of the perineum were selected for the study. During the interview before anaesthesia, informed consent was obtained for the administration of lignocaine and stimulation of the ulnar nerve with an electric current. Premedication, the method of anaesthesia and the methods used to obtain muscle action potentials were identical to those of a previous report (Suzuki et al., 1975).

A pair of rectangular pulses of supramaximal intensity was applied to the ulnar nerve to obtain the recovery curve of the muscle action potential. The first stimulus of the pair is called the “conditioning stimulus” and the second is called the “test stimulus”. The ratio of the amplitude of the muscle response evoked by the test stimulus (M2) to that of the conditioning stimulus (M1) as a percentage was plotted against the interval between these two stimuli (figs 1 and 2). The recording at each pairing interval was accomplished with one application, and each pair of stimuli was applied at 10-s intervals. The interval between the two stimuli forming a pair ranged between 7 and 100 ms, and recordings were made at 1-ms intervals between 7 and 10 ms, and at 20-ms intervals between 10 and 100 ms respectively. After obtaining recovery curves, 30-Hz tetanic stimuli of 10–15 s
duration were applied to examine the responses with or without tetanic fade and post-tetanic potentiation.

Lignocaine hydrochloride 1% in unbuffered physiological saline was infused with a constant infusion pump into the brachial artery. Before the infusion of lignocaine, it was shown that no changes in muscle responses could be found from infusion of physiological saline alone. The infusion rate of the lignocaine solution was controlled to maintain a rate at which the amplitude of a single muscle action potential was depressed to about 80% of the preinfusion value; this varied from 0.34 to 1.7 ml min$^{-1}$ (3.4–17.0 mg min$^{-1}$ respectively). The total dose of lignocaine was between 8 and 14 ml (80 and 140 mg respectively), and the duration of infusion was between 6 and 15 min.

The recovery curves were examined before the infusion of lignocaine, as controls, at various periods during the infusion and during and after the period of recovery from the block in all subjects.

**RESULTS**

An example of the muscle action potentials used to obtain recovery curves is shown in figure 1. The left panel shows a single and paired responses at each interval of stimulation before the infusion of lignocaine, and the right panel shows responses during the infusion. The amplitude of a single muscle action

**FIG. 1.** An example of muscle action potentials obtained in one subject. The left panel shows single and paired responses in the control state, and the right panel shows those during lignocaine infusion. The lower half of the figure (20–100 ms interval of stimulation) is obtained with an oscilloscope sweep speed one-tenth that of the upper half (7–10 ms interval of stimulation).
potential during the infusion of lignocaine in this subject was depressed to 82% of the control, and the amplitudes of responses ($M_2$) to the test stimuli in each determined interval of stimulation were depressed further than the amplitudes of responses ($M_1$) to the conditioning stimuli—$M_2/M_1$ ratio of 68% at 7-ms interval of stimulation and 91% at 100-ms interval of stimulation respectively. The recovery curves obtained from the responses in figure 1 are shown in figure 2. The control curves were identical to those in our previous report, and the recovery curve during the infusion of lignocaine was significantly lower than the control.

The mean ratio of action potential response to test stimuli ($M_2$) against that to conditioning stimuli ($M_1$) at each time interval for paired stimuli and the resulting recovery curves in 10 subjects are presented in table I and figure 3. The control curves are characterized by a slight depression of the response $M_2$ relative to $M_1$ at intervals shorter than 10 ms ($M_2/M_1 = 97.5 ± 3.2%$ at the 7-ms interval), followed by a slight potentiation of the test response $M_2$ to the response $M_1$ at the longer intervals ($M_2/M_1 = 102.4 ± 4.4%$ at the 20-ms and $106.1 ± 1.8%$ at 100-ms intervals). This pattern of the control curve was identical to that obtained previously from 32 subjects (Suzuki et al., 1975) and that shown in figure 2.

When the amplitude of the muscle action potential evoked by the conditioning stimulus ($M_1$) was depressed to 82.2 ± 4.0% of the control during the infusion of lignocaine, the amplitude of the second muscle action potential ($M_2$) was depressed more than that of $M_1$ at each interval estimated less than 100 ms, so that the recovery curve was significantly depressed. Maximum depression of $M_2$ to 55.1 ± 90

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**TABLE I.** The ratios of action potential responses to test stimuli ($M_2$) to that to conditioning stimuli ($M_1$) at various intervals of paired stimuli in 10 subjects. Mean values ± SEM

<table>
<thead>
<tr>
<th>Interval between stimuli (ms)</th>
<th>Control (%)</th>
<th>Lignocaine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>97.5 ± 3.2</td>
<td>55.1 ± 4.8</td>
</tr>
<tr>
<td>8</td>
<td>96.1 ± 3.1</td>
<td>60.1 ± 5.2</td>
</tr>
<tr>
<td>9</td>
<td>97.4 ± 2.9</td>
<td>60.0 ± 5.7</td>
</tr>
<tr>
<td>10</td>
<td>102.3 ± 1.6</td>
<td>60.4 ± 5.8</td>
</tr>
<tr>
<td>20</td>
<td>102.4 ± 4.4</td>
<td>56.9 ± 6.5</td>
</tr>
<tr>
<td>40</td>
<td>106.3 ± 3.6</td>
<td>61.6 ± 6.7</td>
</tr>
<tr>
<td>60</td>
<td>107.0 ± 3.1</td>
<td>68.2 ± 5.7</td>
</tr>
<tr>
<td>80</td>
<td>106.1 ± 1.4</td>
<td>73.7 ± 5.4</td>
</tr>
<tr>
<td>100</td>
<td>106.1 ± 1.8</td>
<td>75.9 ± 5.4</td>
</tr>
</tbody>
</table>

**FIG. 3.** The recovery curves from averaged $M_2/M_1$ ratios in 10 subjects before and during infusion of lignocaine (table I).

4.8% of $M_1$ was noted at the 7-ms interval of stimulation. The depressed $M_2/M_1$ ratios were kept on the same level at an interval of less than 40 ms, and recovered slightly at longer intervals; thus the ratio of $M_2$ to $M_1$ at the 100-ms interval of stimulations was 75.9 ± 5.4%. Complete recovery to control values following the test responses was accomplished in less than 2 s after the conditioning stimuli.

After termination of the i.a. infusion of lignocaine, the recovery time to control values of the depressed muscle action potentials varied. In six of the 10 subjects, recovery curves could be estimated when the amplitude of the muscle action potential in response to the conditioning stimulus ($M_1$) recovered almost to control values (97.3 ± 1.3% of control) but that in response to the test stimulus ($M_2$) did not recover, even following the termination of lignocaine infusion.
Therefore the mean amplitude of responses to test stimuli \( (M_2) \) in this group was depressed also after the infusion of lignocaine, although the depression of \( M_2 \) was less marked than that during the infusion of lignocaine: 68.3 ± 4.0\% of \( M_2 \) at the 7-ms interval and 95.3 ± 4.9\% of \( M_2 \) at the 100-ms interval (fig. 4).

During the depression phase of recovery curves, fade of muscle action potentials was prominent at a frequency of less than 30 Hz during tetanic stimulation. Post-tetanic potentiation was observed, but the degree of the potentiation was less marked than that shown by non-depolarizing muscle relaxants. In some cases (fig. 5), when the amplitude of the muscle action potential was depressed to less than 70\% of control, little or no post-tetanic potentiation was noticed.

### Table II. Mean \( M_2/M_1 \) ratios in six subjects when the amplitude of response to conditioning stimuli \( (M_1) \) recovered to near control values

<table>
<thead>
<tr>
<th>Interval between stimuli (ms)</th>
<th>Control (%)</th>
<th>Lignocaine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>94.2 ± 4.8</td>
<td>68.3 ± 4.0</td>
</tr>
<tr>
<td>8</td>
<td>95.5 ± 3.2</td>
<td>75.3 ± 3.0</td>
</tr>
<tr>
<td>9</td>
<td>97.8 ± 3.7</td>
<td>77.0 ± 3.4</td>
</tr>
<tr>
<td>10</td>
<td>100.8 ± 2.8</td>
<td>80.5 ± 4.2</td>
</tr>
<tr>
<td>20</td>
<td>111.2 ± 2.6</td>
<td>82.2 ± 5.4</td>
</tr>
<tr>
<td>40</td>
<td>115.5 ± 1.9</td>
<td>89.7 ± 6.3</td>
</tr>
<tr>
<td>60</td>
<td>115.8 ± 2.7</td>
<td>95.0 ± 5.6</td>
</tr>
<tr>
<td>80</td>
<td>110.7 ± 3.7</td>
<td>95.2 ± 5.3</td>
</tr>
<tr>
<td>100</td>
<td>111.3 ± 3.1</td>
<td>95.3 ± 4.9</td>
</tr>
</tbody>
</table>

**FIG. 4.** The recovery curves from averaged \( M_2/M_1 \) ratios in six subjects after infusion of lignocaine (table II).

**FIG. 5.** An example of tetanic stimulation with 30-Hz frequency and 15-s duration during lignocaine infusion in one subject. Each record shows the amplitude of single muscle action potentials evoked at intervals of 10 s. The arrow shows the start of tetanic stimulation. During infusion of lignocaine 100 mg, the muscle action potential was depressed to 65\% of control, and the amplitude was depressed further during tetanic stimulation (fade), but no potentiation is seen after the tetanic stimulation.

### DISCUSSION

It has been demonstrated in our previous study (Suzuki et al., 1975) that neuromuscular blocking agents induce two patterns of response in the recovery curves of muscle action potentials in healthy human subjects. During partial paralysis by non-depolarizing agents, the recovery curve is characterized by a potentiation at very short intervals of less than 10 ms and a succeeding prolonged depression (competitive pattern), while the recovery curve following depolarizing agents is characterized by an immediate depression and a succeeding gradual recovery (depolarizing pattern). The authors concluded that these characteristic patterns of recovery curve are thought to be a result of the mode of action of the relaxant at endplate receptors and their adjacent muscle membranes,—either competition or accommodation.

In contrast, the pattern of recovery curves produced by the i.a. infusion of lignocaine in this study was characterized by marked and serial depression of the responses to test stimuli at intervals of 7–100 ms after the conditioning stimulus, although the depressions of the responses to conditioning stimuli were slight (82.2 ± 4.0\% of control in table I and figure 3) or negligible (97.3 ± 1.3\% of control in table II and figure 4). This pattern of recovery curve differs from that produced by both groups of muscle relaxants.

Only two possible mechanisms may be considered to explain the depressed recovery curves in our previous study (Suzuki et al., 1975). One is that the amount of transmitter released from motor nerve
terminals in response to the test stimulus is decreased more than that released by the conditioning stimulus. The other possible mechanism is that there is a temporary decrease in the sensitivity of the post-junctional membranes after an action potential is discharged by the conditioning stimulus.

It has been recognized by some investigators that local anaesthetic agents depress neuromuscular transmission at concentrations lower than those required to block conduction in the nerve axon (Usubiaga and Moya, 1968; Usubiaga and Standaert, 1968; Katz and Gissen, 1969). Of course, local anaesthetics in high concentrations may affect both pre- and post-junctional functions at the neuromuscular junction (Galindo, 1971). However, there are many reports suggesting that the primary site of action with low concentrations is at the motor nerve terminal (Straughan, 1961; Usubiaga and Standaert, 1968; Ekstedt, Stålberg and Thorn-Alquist, 1971; Galindo, 1971). In animal experiments, Blaber (1973) reported that lignocaine in low concentration (42 μmol litre⁻¹) did not exert any post-junctional blocking action, but depressed the rate of refilling of transmitter stores and depleted the stores at high rates of stimulation. In the light of these reports, it seems reasonable to believe that the depressed recovery curve or the decreased test responses with lignocaine are caused by a decrease in the amount of transmitter released from nerve terminals by the test stimulus compared with that released by the conditioning stimulus.

A reduced sensitivity of the post-junctional membrane caused by lignocaine was difficult to disprove directly in this study, although it has been stated that the reduced sensitivity as a result of accommodation did not continue longer than 40 ms after the conditioning stimulus (Suzuki et al., 1975). Moreover, it is believed that the mechanism proposed for the depression of recovery curves should be in keeping with the findings following tetanic stimulation. Post-tetanic potentiation was not as prominent as that found with non-depolarizing muscle relaxants. When a single muscle action potential was depressed to 70% or less of control by lignocaine, there were occasions when no post-tetanic potentiation occurred, although pronounced fade of the action potential was found consistently during tetanic stimulation. These findings with tetanic stimulation have been observed also by Usubiaga and Standaert (1968), Katz and Gissen (1969) and Galindo (1971). It is concluded that the results in this study might be attributed to an action of lignocaine on the motor nerve terminals.

REFERENCES


EFFETS NEUROMUSCULAIRE SUR L'HOMME DE L'INFUSION DE LIGNOCAINE PAR VOIE INTRA-ARTERIELLE

RESUME

Les auteurs de cet article ont étudié à l'aide d'électromyographie évoquée, les effets neuromusculaires de la lignocaine, pendant et après son infusion intra-arterielle sur des adultes en bonne santé. Des stimulants appariés supramaximaux, ont été appliqués au nerf ulnaire, à des intervalles variables entre les deux stimulants. L'amplitude du potentiel de l'action du muscle de l'hypothénar au second composant des stimulants appariés (réaction test) a été comparée à celle évoquée par le premier composant (réaction de conditionnement). Pendant et après l'infusion intra-arterielle de lignocaine, il y a eu des diminutions marquées de la réaction test à des intervalles compris entre 7 et 100 ms après le stimulant de conditionnement, bien que les diminutions de la réaction de conditionnement aient été faibles ou négligeables. Les constatations des réactions test diminuées ont coïncidé avec les résultats obtenus avec la stimulation tétniqune comme par exemple affaiblissement intra-arteriel prononcé et seulement une légère potentiation post-tétanique. Les différences entre ces constatations et celles résultant des relaxants musculaires ont été comparées et on en a conclu que le mécanisme responsable de ces résultats pourrait être attribué à un effet de la lignocaine sur les extrémités des nerfs moteurs.
WIRKUNGEN DER I.A. INFUSION VON LIGNOKAN AUF DIE MUSKELNERVEN IM MENSCHEN

ZUSAMMENFASSUNG

BRITISH JOURNAL OF ANAESTHESIA

EFFECTOS NEUROMUSCULARES POR INFUSION I.A. DE LIGNOCAINA EN EL HOMBRE

SUMARIO
Se estudiaron los efectos neuromusculares de lignocaina durante y después de infusión i.a., en pacientes adultos saludables, empleando electromiografía evocada. Se aplicaron estímulos supramaximos apareados al nervio ulnar con intervalos variables entre los dos estímulos. La amplitud del potencial de la acción muscular hipotenaria al segundo componente del estímulo apareado (respuesta de prueba) fue comparada con aquella evocada por el primer componente (respuesta condicionadora). Durante y después de la infusión i.a. de lignocaina, se presentaron marcadas disminuciones en la respuesta de prueba a intervalos de 7 a 100 ms después del estímulo condicionador, aunque las disminuciones de la respuesta condicionadora resultaron leves o insignificativas. El descubrimiento de respuestas de prueba disminuidas coincidió con los resultados obtenidos mediante estímulo tetánico tales como un debilitamiento pronunciado y una potenciación post-tetánica solo leve. Se compararon las diferencias entre estos descubrimientos y aquellos obtenidos con relaxantes musculares, llegando a la conclusión que el mecanismo responsable de estos resultados podría atribuirse al efecto ejercido por lignocaina sobre los terminales de nervios motores.