Neuroselective Sensory Electrodiagnostic Evaluation of 4% Liposomal Topical Lidocaine

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We used a neuroselective transcutaneous electrical stimulus to determine the onset time of cutaneous anesthesia with 4% liposomal lidocaine under occluded and nonoccluded conditions. The pain tolerance threshold (PTT) was used to atraumatically evaluate nociception. Twenty adult volunteers had liposomal lidocaine applied to the volar surface of each forearm for durations ranging from 0 through 30 min (at 5-min intervals) under occluded and nonoccluded conditions. The PTT was determined using three different frequencies (2000 Hz, 250 Hz, 5 Hz) stimulating Aβ, Aδ, and C fibers, respectively. The time to reach the maximum PTT achieved defined the anesthetic onset time for each frequency. A differential onset of cutaneous anesthesia among the three frequencies was clearly demonstrated, however there was no significant difference in onset time between occluded and nonoccluded conditions. Blockade of C fiber transmission occurred significantly earlier than that of Aδ (P = 0.029), which occurred earlier than that of Aβ (P = 0.001) as determined using the Wilcoxon’s signed rank test. We conclude that a mean onset time of approximately 4 min for blockade of C fiber transmission and 6 min for Aδ fiber transmission suggests that painful stimuli such as venipuncture may be attenuated as early as 7 min.

Methods

After obtaining institutional approval and informed consent, 20 ASA physical status I or II patients were

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recruited for the study. Subjects with a history of chronic or neuropathic pain were excluded. Analgesic use (e.g., opioid, nonsteroidal antiinflammatory drugs) was recorded. Before beginning the study, the subjects were asked to assess their pain tolerance as being low, medium, or high. The volar surface of each forearm was divided from distal to proximal into 7 areas corresponding to 0- (control), 5-, 10-, 15-, 20-, 25-, and 30-min application times of 4% liposomal lidocaine. A 6-mm thick layer of 4% liposomal lidocaine was applied to 6 areas of each forearm using a template with 2 × 4-cm segments cut out to allow for coverage beyond the area of the electrodes. After each application time, the area was wiped clean, electrodes applied, and PTT determinations made at frequencies of 2000 Hz, 250 Hz, and 5 Hz. Subjects were randomized to have either the right or left arm receive the occluded application to obviate possible dominant arm biases. Subjects were blinded to the PTT value generated at each time point. The current was delivered to the skin by a pair of gold surface electrodes 1 cm in diameter that were separated by 1.7 cm with a clear Mylar spreader (Neurotron Inc). The stimulating surface of each electrode was covered with a thin film of electroconductive gel.

The subjects self-administered the PTT by depressing a button and releasing it when the stimulus was no longer tolerable. The subject was instructed to stop each measurement for pain at the same intensity as was felt at baseline. This procedure was repeated at each of the three frequencies on each of the 7 areas tested per arm. The stimulus delivered at each frequency was delivered in a stepwise fashion starting from 0.001 mA and progressing to a maximum of 9.99 mA, after which the stimulus automatically shut off. If a subject were to reach the maximum threshold at any given time point, then the test was repeated for that time point with the instruction to release the button when the stimulus was first perceived. This was defined as the pain perception threshold. In instances where the maximal PTT was achieved, the time to the maximal pain perception threshold was then regarded as the onset time for that frequency. Subjects were asked to describe the character of each frequency and to assess if any one frequency was more objectionable than another.

The sample size was based on the primary end point of comparing the time to maximal threshold between the occluded and nonoccluded applications to achieve at least 80% power to detect a difference of more than 0.7 SD at a significance level of $P = 0.05$ (9). The data were analyzed by mean ± SD, median, and interquartile range. Comparisons between the times to reach the maximal PTT between frequencies and between occluded and nonoccluded applications at a given frequency were performed using the Wilcoxon’s signed rank test (9,10). The stimulus duration for each stepwise increase in intensity is a linear function of its frequency with 2000 Hz taking 0.5 s, 250 Hz taking 1 s, and 5 Hz taking 2 s (3). Therefore, the stimulus duration was normalized for the purpose of interfrequency comparisons (the times for 5 Hz and 250 Hz were multiplied by 0.25 and 0.5, respectively) (3). A $P$ value $<0.05$ was considered significant.

### Results

Twenty subjects completed the study. The demographic variables are presented in Table 1. The maximum tolerated threshold compared with baseline values is presented in Table 2 and was significantly larger ($P < 0.0001$; Wilcoxon’s signed rank test) for all frequencies under both occluded and nonoccluded conditions. The time to reach the maximally tolerated threshold and comparisons between frequencies and conditions are presented in Figure 1. The mean onset times for 2000 Hz, 250 Hz, and 5 Hz stimulus frequencies and occluded/nonoccluded conditions were 9.8 ± 6.6/12.0 ± 8.2 min, 6 ± 4.1/7.0 ± 3.2 min, and 3.8 ± 2.2/4.1 ± 2.4 min, respectively. There was no significant difference found between occluded and nonoccluded conditions. There was no consistency between the self-classification of pain tolerance and actual stimulus tolerance.

At the maximum thresholds reached, the subjects described the 2000 Hz stimulus as a deep pressure sensation, and many (30%) were able to tolerate the maximum output of 9.99 mA. The 250 Hz stimulus was described as a sharp needle sensation and was the most objectionable of the three frequencies tested. The 5 Hz stimulus was described as a burning sensation, which would persist for several seconds after discontinuing the stimulus. There were several instances where muscle twitching was elicited, and for some subjects, this was more objectionable than the stimulus.

### Discussion

The intention of this preliminary study was to document the onset of a differential cutaneous blockade

<table>
<thead>
<tr>
<th>Table 1. Demographic Data</th>
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<tr>
<td><strong>Age (yr)</strong></td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
</tr>
<tr>
<td>Caucasian*</td>
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<tr>
<td>16</td>
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</table>

* Two individuals between the ages of 55–63 did not give their ages.
* $P = 0.001$ ($t^2$, df = 3).
could be used singularly for future evaluations of anesthesia. This suggests that the 250 Hz stimulus was described as a burning sensation, a characteristic typically ascribed to Aβ fibers. The 5 Hz stimulus was described as a burning sensation, a characteristic stimulus transmitted by C fibers (11). Consistent with these differential sensations, there was a differential onset of anesthesia. This suggests that the 250 Hz stimulus could be used singularly for future evaluations of cutaneous anesthesia because this was the most objectionable and perhaps the most clinically relevant for a variety of painful procedures. A limitation of this technique was occasional direct muscle stimulation. This occurred when the electrodes were placed directly over the radial or ulnar nerve distribution and was avoided when the electrodes were placed medially to each nerve.

A potential advantage of using noxious electrostimulation to assess cutaneous anesthesia rather than traditional noxious stimulation such as heat stimuli is that electrical stimulation activates afferent axons directly, bypassing peripheral nociceptors and is therefore independent of receptor processes such as sensitization (3,12). Another potential advantage is that there is evidence that habituation does not occur with this technique1. This nonhabituation may also be consistent with the electrical stimulus bypassing the peripheral nociceptors. These findings now require corroboration with a clinical measure such as pinprick to validate the utility of a neuroselective transcutaneous electrical stimulus in evaluating cutaneous anesthesia.

In summary, this is the first report on the use of a neuroselective transcutaneous electrical stimulus. Sine wave stimuli at the frequencies of 2000 Hz, 250 Hz, and 5 Hz stimulated the three major sensory nerves Aβ (cutaneous touch, pressure), Aδ (mechanoreceptors, touch, fast pain), and polymodal C fibers (slow pain, temperature, postganglionic sympathetic) (4,5). It was expected, as with neuraxial blockade with local anesthetic, that the unmyelinated C fibers would be blocked first, followed by the myelinated Aδ fibers, and lastly blocking conduction in the large Aβ fibers (4,7). Interestingly, the subjects uniformly described the character of each frequency stimulus. The 2000 Hz stimulus elicited a deep pressure sensation, which is a stimulus transmitted by Aβ fibers. The 250 Hz frequency was described as a sharp, stabbing, needlelike pain, which is a characteristic typically ascribed to Aδ fibers. The 5 Hz stimulus was described as a burning sensation, a characteristic transmitted by C fibers (11). Consistent with these differential sensations, there was a differential onset of anesthesia. This suggests that the 250 Hz stimulus could be used singularly for future evaluations of cutaneous anesthesia because this was the most objectionable and perhaps the most clinically relevant for a variety of painful procedures. A limitation of this technique was occasional direct muscle stimulation. This occurred when the electrodes were placed directly over the radial or ulnar nerve distribution and was avoided when the electrodes were placed medially to each nerve.

Table 2. Maximum Tolerated Threshold Compared to Baseline

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Threshold (mA)</th>
<th>Occluded</th>
<th>P* value</th>
<th>Nonoccluded</th>
<th>P* value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 Hz</td>
<td>Baseline: mean ± sd</td>
<td>5.69 ± 2.48</td>
<td>5.49 ± 1.92</td>
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<tr>
<td></td>
<td>Maximum: mean ± sd</td>
<td>7.40 ± 2.34</td>
<td>7.85 ± 2.10</td>
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<tr>
<td>250 Hz</td>
<td>Baseline: mean ± sd</td>
<td>2.21 ± 1.72</td>
<td>2.00 ± 1.14</td>
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<tr>
<td></td>
<td>Maximum: mean ± sd</td>
<td>3.89 ± 2.49</td>
<td>4.22 ± 2.49</td>
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<tr>
<td>5 Hz</td>
<td>Baseline: mean ± sd</td>
<td>1.68 ± 1.70</td>
<td>2.22 ± 1.64</td>
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<tr>
<td></td>
<td>Maximum: mean ± sd</td>
<td>1.83 ± 1.98</td>
<td>1.45 ± 0.99</td>
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<tr>
<td></td>
<td>Δ ± sd</td>
<td>1.51 ± 0.96</td>
<td>2.05 ± 1.53</td>
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</table>

Δ = difference between baseline threshold and maximum threshold.
*P for Wilcoxon’s signed rank test.

Figure 1. Box plot of time to maximal threshold at each frequency. The format presents the first and third quartiles as the top and bottom of the box. The line and whiskers represent the mean and sd. The broken line represents the median. (P < 0.05 for occluded versus nonoccluded at each frequency. Wilcoxon’s signed rank test was used to determine P values). * 2000 Hz versus 250 Hz was 0.029 (occluded P) and 0.013 (nonoccluded P). 2000 Hz versus 5 Hz was 0.001 (occluded P) and <0.001 (nonoccluded P). 250 Hz versus 5 Hz was 0.019 (occluded P) and <0.001 (nonoccluded P).
References


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