Altered Neural Conduction with Epidural Bupivacaine

Joseph F. Cusick, M.D.*, Joel B. Myklebust, Ph.D.,† Stephen E. Abram, M.D.,‡ Arthur Davidson, M.D.§

The sites and magnitude of evoked potential response alterations induced by varying masses and concentrations of epidurally administered bupivacaine were assessed from electrodes positioned along the conducting pathways of the monkey. The mass of bupivacaine was the major factor in determining the level and degree of response alterations. At the lower levels of total drug mass, effects were limited to the dorsal root entry zone, whereas higher levels of mass not only increased the response attenuation at the gray matter level but resulted in additional changes in those responses recorded from the spinal cord white matter tracts. With all other factors stable, increasing concentration was associated with a greater degree of response attenuation, especially at the lower levels of total mass. These findings indicate that the mass of the drug is the major factor in determining the magnitude and level of bupivacaine-induced epidural analgesia. Increased concentration influences the local anesthetic's penetration at the dorsal root entry zone and, to a lesser degree, at the white tracts of the spinal cord. (Key words: Anesthetic techniques: epidural. Anesthetics, local: bupivacaine. Spinal cord: evoked potentials.)

IN A PREVIOUS PUBLICATION, we described an animal model capable of demonstrating selective sites of altered electrophysiologic activity induced by different epidurally administered local anesthetics.1 That study, however, did not clarify the possible contributions of factors such as local anesthetic concentration or total drug dose (mass). Clinical observations indicate that the intensity of epidural blockade is dependent upon the mass with certain investigators noting that the total mass of an epidural anesthetic required to block one spinal segment is almost constant at a given age.2,3 The differential quality of such epidural blockades, especially their temporal characteristics, however, usually do not demonstrate a strict linear correlation with mass, but, instead show a staggered pattern of rises in blockade intensity.2,3 These findings suggest that the differential neural effects of various epidurally applied local anesthetics are dependent upon critical levels of the mass of the drug.

To clarify this concept and to extend our observations regarding the mechanisms of epidural anesthetic action, the selective electrophysiologic alterations induced by varying total masses and concentrations of bupivacaine have been examined. Bupivacaine was selected because of its wide clinical acceptability, and its previously noted effects at varying levels of the evoked potential conducting pathways.1

MATERIALS AND METHODS

Varying masses and volumes of bupivacaine were administered epidurally to adult (8–10 kg) stump-tail macaque monkeys (Macaca arctoides) which had electrodes placed along the evoked potential conducting pathways in a previously described manner.1 Responses evoked by sciatic nerve (SN) stimulation recorded from cauda equina (SN → CE), bilaterally from conus medullaris (SN → CM), upper thoracic cord (SN → Thc), and sensorimotor cortices (SN → SMC) were measured using previously described stimulation and recording parameters.1

Additionally, responses evoked by conus medullaris stimulation were recorded from upper thoracic cord to evaluate dorsal column conduction (CM → Thc or cord → cord), and responses evoked by sensorimotor cortex stimulation were recorded at the conus medullaris level to evaluate corticospinal tract conduction (SMC → CM). Restlessness during the recording was alleviated by intravenous subanesthetic doses of sodium thiamylal in amounts (2–2.5 mg) well below levels known to affect evoked responses.1,5 These responses were retrieved with CTC-2000 Evoked Potential Measuring System.† The varying concentrations and total doses of bupivacaine were injected into the epidural space through a 19-gauge catheter with its tip positioned at the L2 level. Relevant data from our previous report relating to animals receiving epidurally administered bupivacaine including those with different total doses and concentrations were used in this study.1 In addition, seven monkeys were given four to five separate trials with varying concentrations and volumes of bupivacaine. The total number of trials at each drug mass and concentration are shown in figure 1. Functional effects of the epidural blockade were monitored by use of the withdrawal reflex elicited by noxious stimuli applied to dorsal aspects of the foot and hand as the determinant of analgesia, and flaccid paralysis as the determinant of motor block.

ANALYSIS

In order to compare the present findings with previous data, the per cent reduction in evoked response amplitudes recorded at varying sites were plotted against time.

† Clinical Technology Corporation, Kansas City, Missouri 64114.
Comparison of values in figure 3 diagonally oriented from left to right (Column 1) demonstrates the effect of increasing concentration and mass with volume constant. Comparison of values in the vertically oriented columns (Column 2) demonstrates the effect of increasing concentration and decreasing volume while keeping local anesthetic mass constant. Comparison of the values in the horizontally oriented columns (Column 3) demonstrates the effect of increasing volume and total mass while maintaining a constant concentration.

Figure 4 and the values in column 1 of figure 3 show the degree of amplitude reduction induced by varying the concentrations and masses with volume constant (3 ml). The 0.25 per cent concentration (mass of 7.5 mg) essentially limits its effects to the dorsal root entry zone region with changes, at that level, that are comparatively of lesser duration and magnitude than those alterations noted with the 0.5 per cent (mass of 15 mg) and 0.75 per cent (mass of 22.5 mg) concentrations. Although the duration of the response alterations are slightly increased with the 0.75 per cent concentration (mass of 22.5 mg), figures 3 and 4 indicate that the degree of decreased response amplitude at the dorsal root entry zone (SN → CM) and the dorsal columns (CM → Thc) was quite similar for both the 0.5 per cent (mass of 15 mg) and the 0.75 per cent (mass of 22.5 mg) concentrations. Comparison of the response amplitude changes recorded from both of the dorsolaterally positioned conus medullaris electrodes, however, shows a greater symmetry of response changes at the dorsal root entry zone (SN → CM) with the 0.75 per cent (mass of 22.5 mg) concentration than those found with the 0.5 per cent (mass of 15 mg) concentration which frequently showed unilateral discrepancies of 20–30 per cent in response amplitude reduction. In contrast to the progressive character of decreasing amplitude of the primary response components

In order to reduce possible intersubject variability, the majority of data for each plot was taken only from animals in which all three components of the experimental protocol (concentration, mass, and volume) had been previously selected. Additionally, to offer improved descriptive analysis of each of the present results and to improve comparison with future relevant studies, the response amplitudes within each group were divided by control amplitude and the values expressed as per cent reduction of amplitude (fig. 2). The amplitude reduction integrated over time (area of shaded region, N₁, fig. 2) is taken as a measure of the total drug effect upon the evoked response. For ease of comparison, this value (N₁) is normalized by dividing it by the total area (100 per cent amplitude reduction up to 240 min, N₂). This analysis can be defined as:

\[
\frac{R_1\Delta t + R_2\Delta t + \cdots + R_n\Delta t}{n\Delta t}
\]

where \( n \) is the total number of observation periods, \( R_i \) is the per cent reduction in the \( i^{th} \) period, and \( \Delta t \) is each 0.5-hour period.

**Results**

In all trials, the wide variability of the response alterations recorded at the cauda equina level evoked by sciatic nerve stimulation (SN → CE) excluded their inclusion in the descriptive analysis of the results. It must be noted, however, that changes at the cauda equina level usually occurred earlier or concurrently with dorsal root entry zone alterations (SN → CM) and were almost consistently of lesser magnitude and duration than corresponding alterations at the dorsal root entry zone or spinal cord levels.

Figure 3 shows the per cent reduction in mean response amplitude integrated over time for each of the combinations of drug volume, concentration, and mass.

**Fig. 2.** Distribution profile of the analysis method used to obtain comparative values of evoked response amplitude reduction. Area N₁ which represents the degree of reduction is normalized by dividing it by the total area corresponding to 100 per cent amplitude reduction over 240 minutes (N₂).
found at the dorsal root entry zone (SN → CM) and the dorsal columns (CM → Thc), the responses recorded at the conus medullaris evoked by sensorimotor cortex stimulation (SMC → CM) demonstrated greater variability and a lesser degree of progression relative to increasing concentrations and total doses (figs. 3 and 4). The recovery of these lateral spinal column responses (SMC → CM), however, did not correlate with a similar recovery from flaccid paralysis which usually continued for an additional 20 to 30 minutes.

Figure 5 and Column 2 of figure 3 show the degree of evoked response alterations resulting from administering the same total mass (15 mg) derived from varying the volumes of the different concentrations. At the dorsal root entry zone level (SN → CM), all three concentrations resulted in fairly similar degrees of decreased amplitude and response distortion. Evidence of altered con-

AMPLITUDE REDUCTION

A. SCHEMATIC

<table>
<thead>
<tr>
<th>TOTAL DOSE (mg)</th>
<th>7.5</th>
<th>15</th>
<th>22.5</th>
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<tbody>
<tr>
<td>CONCENTRATION (%)</td>
<td>.25</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>.50</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>.75</td>
<td>34</td>
<td>64</td>
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B. SN → CM

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<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>.75</td>
<td>64</td>
<td>95</td>
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C. CM → THC

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D. SMC → CM

<table>
<thead>
<tr>
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FIG. 3. The normalized values for response amplitude reduction obtained through the method described in figure 5. (A). Schematic shows the orientation of values relative to varying concentrations and masses. The values in the horizontal direction, as depicted in column 1, show the alterations induced by varying masses of epidurally administered bupivacaine with concentration constant. The values in the vertical direction, as depicted by column 2, show the alterations induced by varying concentrations with total dose constant. The values in the diagonal direction, as depicted in column 3, show the changes induced by varying concentrations and masses of a constant volume of epidural bupivacaine. (B). Analysis of the data obtained from the response alterations recorded from conus medullaris (CM) evoked by sciatic nerve (SN) stimulation (SN → CM), indicating the degree of impaired activity at the dorsal root entry zone. (C). Similar presentation of the data recorded at the upper thoracic cord (Thc) evoked by conus medullaris (CM) stimulation (cord → cord), indicating degree of impaired dorsal column conduction. (D). Similar presentation of data recorded at conus medullaris (CM) evoked by sensorimotor cortex (SMC) stimulation (SMC → CM), indicating the degree of impaired corticospinal tract conduction.

Fig. 4. Percentage changes in amplitude induced by epidurally administered bupivacaine in varying concentrations (0.25, 0.5, and 0.75 per cent) and mass (7.5, 15, and 22.5 mg) with constant volume (3 ml). (Upper) Summation of data measuring peak-to-peak amplitude changes from control (inset) of conus medullaris (CM) responses evoked by sciatic nerve (SN) stimulation (SN → CM), indicating dorsal root entry zone activity. (Middle) Similar presentation for amplitude changes of responses recorded at the upper thoracic spinal cord evoked by conus medullaris stimulation (CM → cord), indicating dorsal column conduction. (Lower) Similar response changes recorded at conus medullaris (CM) evoked by sensorimotor cortex (SMC) stimulation (SMC → CM), indicating corticospinal tract conduction. Standard error of the mean did not exceed 10 per cent for any of the data measurements.

duction through the dorsal columns (CM → Thc) and lateral columns (SMC → CM), however, indicate a slightly greater effect with the 0.5 per cent and 0.75 per cent concentrations, especially on the lateral columns.
and concentration (0.5 per cent). These response alterations in this present study, including this latter group, did maintain a consistent relationship within each animal as well as in their comparison to other animals. This factor and the limited data within each group does not permit a determination of any valid statistical difference that could be attributed to this portion (SMC → CM) of figure 5.

Figure 6 and Column 3 of figure 3 illustrate the response alterations noted with the different masses of the drug derived by changing the volume of a single concentration (0.5 per cent). The degree of response amplitude reduction and its duration is almost totally dependent upon the mass of bupivacaine. Comparison of these results with the response alterations relative to each total mass and its respective concentration does show that at the lower mass (7.5 mg), the major influencing factor appears to be the increasing concentration of bupivacaine (fig. 3). As the total mass is increased (15 mg and 22.5 mg levels) and the response alterations become more pronounced, however, this influence of increasing concentration does not appear to remain an important factor (figs. 3, 4, 5, and 6).

Discussion

These studies support previous observations that the major effects of epidurally administered bupivacaine occur at the spinal cord level.1–5 Although alterations of response waveform and latency were noted at the cauda equina level, these changes were not only inconsistent but were almost always of lesser magnitude and duration than corresponding response alterations noted at the spinal cord level. These findings which were noted in our prior study1 suggest that structures distal to the spinal cord along the conducting pathway such as peripheral nerve, dorsal root ganglion, or intrathecal nerve roots are not major participants in epidural bupivacaine blockade.

When volume is held constant and increasing concentrations are associated with increasing mass of the drug, bupivacaine in its lowest concentration of 0.25 per cent (mass of 7.5 mg) essentially limited its effects to the dorsal root entry zone (figs. 3 and 4). The magnitude of these response alterations was greater with increased mass and concentration, but the proportionality of these changes was less-pronounced at the higher levels of mass and concentration (fig. 3). However, comparison of response changes recorded from both posterolaterally positioned conus medullaris electrodes showed a consistently symmetrical degree of response attenuation with the 0.75 per cent concentration (mass of 22.5 mg). These findings suggest an increased penetration into the dorsal
horn gray matter with both increasing concentration and total mass. At this juncture, it is important to recognize that the major component of the averaged evoked responses recorded from these dorsal root entry zone regions represents terminating cutaneous and muscle afferent fibers of the group II and III type as well as their internuncial and relay cells.

Therefore, the major portion of this primary response reflects excitation of interneurons mostly in lamina IV and V of Rexed, whereas the majority of afferent fibers for nociception terminate in more superficial lamina. In the present laboratory preparation, the rapid onset of response alterations at the dorsal root entry zone following instillation of the epidural bupivacaine did not permit correlation with a functional evaluation of pain sensation. In all situations, the mass of the local anesthetic agent was the primary determinant influencing the depth of penetration into the dorsal horn gray matter.

The degree of impaired conduction in long tracts of the dorsal and lateral columns was also greatly influenced by the mass of the drug, but the lateral column responses were not affected to the consistent degree found at the dorsal column or gray matter levels. The degree and duration of response attenuation at the lateral column level (SMC → CM), indicative of the physiologic integrity of the corticospinal tract, was consistently less than the presence of lower extremity flaccid paralysis. This functional motor loss more closely approximated the response amplitude reduction noted at the dorsal root entry zone, suggesting that a portion of the motor paresis during bupivacaine blockade is secondary to local anesthetic action at interneurons in the dorsal horn gray matter. In this regard, Hoff demonstrated that the cat corticospinal tract activates anterior horn cells entirely through internuncials located in the dorsolateral gray matter. Although there is anatomic and physiologic evidence in monkeys and humans that a few corticospinal fibers end directly upon anterior horn cells, the majority act through gray matter internuncials. These motor findings and the enhancing influence of higher concentration (0.75 per cent) noted at the dorsal root entry zone with the lower mass (7.5 mg) suggest that concentration may offer increased penetrability into the dorsal horn gray matter. This property may well result in effects not only on those internuncial fibers responsible for evoked response transmission after peripheral nerve stimulation but also internuncial fibers responsible for corticospinal activation of the anterior horn cells. This effect of concentration, however, assumes a lesser importance as the total mass of bupivacaine increases.

The findings of this study certainly emphasize the importance of the mass of the drug in achieving altered neural conduction during epidural bupivacaine blockade as well as demonstrate some influence of drug concentration, especially at lower levels of total mass. It must be noted, however, that the design of the model resulted in a standardized catheter tip positioning at the L1–L2 level with the animal maintained in an essentially horizontal supine position. It may be that neural alterations are influenced by this catheter positioning which is not possible to replicate clinically in a consistent manner. More importantly, it must be remembered that this study...
was conducted using only bupivacaine and, therefore, extending these findings to explain the mechanism of action of other epidurally administered local anesthetics may not be warranted.

References


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