Differential Neural Effects of Epidural Anesthetics

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The purpose of this investigation was to clarify in a laboratory model the sites of action of epidurally administered local anesthetics. This report describes such a model, which is capable of monitoring sites of altered electrophysiologic activity induced by epidural anesthetic agents. Evoked potential response alterations measured from electrodes positioned along the conducting pathways were assessed in six monkeys following epidural injections of 0.5 per cent bupivacaine, 3 per cent chloroprocaine, and 1 per cent etidocaine. Bupivacaine in ten studies was found to cause its major effects at the dorsal root entry zone and the long tracts of the spinal cord white matter, associated with variable peripheral nerve alterations. Chloroprocaine effects in six studies were limited to alteration of responses recorded from the dorsal root entry zone and peripheral nerve. In contrast, etidocaine in eight studies caused marked attenuation of the responses recorded from the long tracts of the spinal cord white matter, associated with only minimal corresponding change at the dorsal entry zone or peripheral nerve levels. These findings illustrate the capability of this experimental model to demonstrate relatively selective effects along the sensory and motor pathways for epidurally injected local anesthetic agents. (Key words: Anesthetic techniques; epidural, sites of action. Anesthetics, local: bupivacaine; chloroprocaine; etidocaine. Spinal cord: evoked potentials.)

IN THE EVALUATION of the mechanisms of action by which local anesthetic agents achieve epidural analgesia, the majority of investigators have used models based on chemical drug assays, or radiopaque contrast medium or isotope tracer studies.1 2 These studies greatly assist in clarifying the sites of local epidural anesthetic concentration, but offer little information concerning the relative anesthetic susceptibility of the various neural structures that have been implicated as sites of action. Because of this lack of information, and because of its potential laboratory and clinical significance, averaged evoked potential alterations recorded from electrodes spaced along the conducting pathways of the monkey were evaluated during epidural blockades with a selection of local anesthetics.

The rationale of this approach is based upon the ability of signal-averaging techniques to measure electrical responses evoked in the nervous system by fixed external stimuli. This form of neurophysiologic monitoring through evaluation of certain alterations of the evoked response character or latency, therefore, offers a method for the assessment of the functional integrity of peripheral nerves, nerve roots, and spinal cord during epidural blockade.

Methods

Six stumptail Macaca arctoides (5–7 kg) underwent electrode implantation while anesthetized with thiopental sodium (10 mg/kg). Electrode pads consisting of three platinum iridium disks, 0.025 mm thick, 2 mm in diameter, and 4 mm apart on center, imbedded in Dacron®-reinforced Silastic®, 0.25 mm thick, were positioned through small incisions in the interlaminar ligamentum flavum into the dorsal midline epidural space over the cauda equina (L4–L5) and upper thoracic cord (T2–T4). At the level of the conus medullaris (T12–L1), three silver ball electrodes 1.5 mm in diameter, connected to individual Teflon® coated stainless steel leads, 0.0125 mm in diameter, were inserted bilaterally into the dorsal epidural space. A radiopaque Teflon catheter, 19-gauge, was also inserted into the epidural space at lumbar levels (L4–L5) with positioning of the tip at the L2 vertebral level. The small openings in the ligamentum flavum were then sealed with small pieces of gelatin sponge and methylmethacrylate. The electrode connectors and the catheter were placed in individual lateral subcutaneous pockets. Additionally, in each monkey, platinum disk electrodes were implanted bilaterally in the epidural space over the sensorimotor cortex. Methylmethacrylate was used to fill the trephine holes and for fixation of the recording leads (fig. 1).

After a one- or two-day recovery period, recordings were carried out before and after injection of one of three epidural anesthetic agents, bupivacaine (0.5 per cent), chloroprocaine (3 per cent), and etidocaine (1 per cent). These three local anesthetics were selected because of their common clinical usage, different physical characteristics (pK, lipid solubility, or ester versus amide linkage), and diverse clinical effects (latency, duration, and degree of motor block).1 Additionally, the concentrations chosen produce both motor and sensory blockade, and were felt to be similar in effectiveness in producing surgical anesthesia.

Each agent was evaluated on two separate occasions in at least three animals, which resulted in ten studies with 0.5 per cent bupivacaine, six studies with 3 per cent chloroprocaine, and eight studies with 1 per cent
etidocaine. All recordings included in the analysis of results were obtained six days or less after electrode implantation, because on two occasions recordings obtained at the eight-day interval proved to be inconsistent. These failures probably reflected changes in the structural integrity of the epidural space, and suggest a temporal restriction of the model's reliability. After intravenous injection of thiamyal sodium (10 mg/kg), the animals were placed in a restraining frame and the previously implanted electrode connectors and epidural catheters were exteriorized. Following recovery from the anesthesia, restlessness was alleviated by intermittent intravenous administration of subanesthetic doses of thiamyal sodium, well below levels known to affect evoked responses.4,5

The sciatic nerve was stimulated transcutaneously using rectangular pulses of 0.2-msec duration at 4 Hz with intensities well above those necessary to obtain a motor response in the hind limbs. These stimuli do not appear to cause discomfort in small animals, nor have they been reported as unpleasant by our patients. A similar stimulus was used for stimulation of the conus medullaris and sensorimotor cortex via the electrodes previously positioned at these levels, which functioned as both stimulating and recording electrodes.

Following sciatic, spinal cord, or sensorimotor cortex stimulation, potentials were assessed to obtain maximum responses. Evoked potentials were retrieved with the CTC-2000 Evoked Potential Measurement System.§ The number of sweeps was kept at 100, and electrode impedance was maintained between 800 and 1200 Ω.

Rectal temperature was kept between 37 and 38.5°C with a thermal blanket. The rate and quality of respirations were carefully observed, and the electrocardiogram was continuously monitored. Neither blood pressure determinations nor arterial blood sampling were performed because of the unacceptable probable incidence of vascular complications and additional discomfort resulting from repetitive arterial cannulations in these sequential studies. Additionally, it has been demonstrated that profound and prolonged ischemia is necessary before evoked potentials recorded from the peripheral nerve or spinal cord are altered.6-8

After control recordings were obtained, 3.0 ml of the selected anesthetic agent was injected via the catheter into the lumbar epidural space. Responses evoked by sciatic nerve stimulation were recorded from the cauda equina, conus medullaris, upper thoracic cord, and sensorimotor cortex. Responses evoked by conus medullaris stimulation were recorded from the upper thoracic spinal cord and sensorimotor cortex. Responses evoked by sensorimotor cortex stimulation were recorded bilaterally from the lateral conus medullaris. The functional effects of each specific epidural blockade were grossly monitored by use of the withdrawal reflex as the determinant of analgesia and flaccid paralysis as the determinant of motor block. The onset and recovery of these modalities were correlated with the corresponding evoked potential alterations.

The maintenance of the integrity of the epidural space was verified by radiographic confirmation using epidural injections of 5 ml of the water-soluble contrast medium metrizamide (Amipaque®) in a concentration of 170 mg iodine/ml. Neither epidural nor

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subarachnoid injections of this contrast agent have resulted in tissue changes with metrizamide concentrations of less than 300 mg iodine/ml.8,10 Metrizamide studies were performed after the first one to two days of recording in three animals, and at the completion of the study in all animals. No change in the consistency of the response alterations was found to result from these myelographic studies.

Results

Bupivacaine (Marcaine®)

Instillation of 0.5 per cent bupivacaine resulted in response alterations most prominent at the level of the conus medullaris, where activity is recorded from entering afferent fibers appropriate to the stimulated nerve, as well as the internuncial and relay cells of the dorsal horn gray matter (dorsal root entry zone), and the long fiber tracts of the spinal cord white matter (fig. 2). Initially (5–12 min), the dorsal root entry zone response relative to the stimulated nerve showed progressively increasing latency and distortion, and decreasing amplitude, of the primary components (figs. 2 and 3). Almost simultaneously with these events, comparable attenuation of lesser duration was observed in the responses recorded from the upper thoracic cord evoked by conus medullaris stimulation, and responses recorded from the lateral conus medullaris evoked by sensorimotor cortex stimulation (figs. 2 and 4).

Fig. 2. Alterations of evoked potential responses induced by epidural injection of bupivacaine (0.5 per cent) and recorded from the electrode sites diagrammed in figure 1. Recordings from the caudal equina (CE) evoked by sciatic nerve (SN) stimulation (SN → CE) showed moderate distortion and loss of amplitude. The most significant and sustained response alteration was found in the gray matter of the spinal cord at the dorsal root entry zone level (SN → CM). Responses conducted along spinal cord white matter fiber tracts (cord → cord and SMC → CM) showed response attenuation that was of comparably lesser degree and duration. Stimulus and initiation of response at arrows.

Fig. 3. Percentage changes of amplitude induced by epidurally administered 0.5 per cent bupivacaine (ten trials), 5 per cent chlorprocaine (six trials), and 1 per cent etidocaine (eight trials) of the conus medullaris (CM) responses evoked by sciatic nerve (SN) stimulation against time, as determined by peak-to-peak measurements (int). Standard deviation did not exceed 10 per cent for any of the measured points. Bupivacaine caused the most profound and sustained response attenuation at this level of the spinal cord gray matter (dorsal root entry zone).
Fig. 4. Percentage changes of amplitude induced by epidurally administered 0.5 per cent bupivacaine (ten trials), 3 per cent chloroprocaine (six trials), and 1 per cent etidocaine (eight trials) of the responses recorded from the dorsal and lateral spinal cord columns against time. Upper, summation of data measuring peak-to-peak amplitude changes from control (inset) of the upper thoracic spinal cord responses evoked by conus medullaris (CM) stimulation (cord → cord) indicating dorsal column conduction. Standard deviation did not exceed 10 per cent for any of the data measurements. Lower, similar presentation for amplitude changes of responses recorded at conus medullaris (CM) evoked by sensorimotor cortex (SMC) stimulation (SMC → CM), indicating corticospinal tract conduction.

The cortical recordings underwent correlating alterations. Responses from the cauda equina evoked by stimulation of the sciatic nerve had the greatest standard deviation of all the responses evaluated in these studies (fig. 5). The inconsistency of these cauda equina amplitude reductions occurred within the same experimental preparations, with reductions ranging from 20 per cent to 70 per cent of the control values.

This information suggests that the most consistent sustained elements of epidural bupivacaine blockade occur at the dorsal root entry zone and, to a slightly lesser extent, at the level of the spinal cord white matter. The loss of the withdrawal reflex and onset of flaccid paralysis correlated with the described evoked response alterations. The recovery of these functional effects, however, was delayed in comparison with the substantial recovery of the evoked responses, and flaccid paralysis persisted for approximately 20 to 30 min after the evoked responses had essentially returned to control amplitude and latency.

CHLOROPROCaine HYDROCHLORIDE (Nesacaine®)

The influence of 3 per cent chloroprocaine on the conus medullaris responses (dorsal root entry zone) evoked by sciatic nerve stimulation showed slightly increased latency, moderate distortion, and decreased amplitude of the primary components (figs. 3 and 6). Corresponding alterations in latency associated with changes of response character were found in the cauda equina responses evoked by sciatic nerve stimulation. These findings were associated with correlating attenuation of the cortical response evoked by sciatic nerve stimulation. Upper thoracic responses evoked by conus medullaris stimulation and conus medullaris responses evoked by sensorimotor cortex stimulation showed no significant alteration (fig. 4).

These findings indicate the maintenance of physiologic integrity of the dorsal, dorsolateral, and lateral spinal columns, and suggest that the major area of blockade with 3 per cent chloroprocaine is at the dorsal root entry zone and, to a lesser extent, at the level of the cauda equina (figs. 3, 5, and 6). The selective alterations of neural conduction at the dorsal horn gray matter of the conducting pathways were more profound than those seen with 1 per cent etidocaine, but less in duration and degree than found with 0.5 per cent bupivacaine (fig. 3). The loss of the withdrawal reflex correlated with the onset of evoked response alterations at the dorsal root entry zone, but recovery of this reflex as an end point of analgesia was delayed relative to the substantial recovery of these evoked re-

Fig. 5. Percentage changes of amplitude induced by epidurally administered 0.5 per cent bupivacaine (ten trials), 3 per cent chloroprocaine (six trials), and 1 per cent etidocaine (eight trials) of the responses evoked by sciatic nerve (SN) stimulation against time, as determined by peak-to-peak measurements (inset). The vertical lines indicate the standard deviation, which demonstrates the variability of amplitude reduction during bupivacaine blockade of the peripheral nerve component of the evoked response pathway.
sponses. The onset and duration of flaccid paralysis were difficult to establish because it was frequently fragmentary and non-uniform.

**Etidocaine (Duranest®)**

Following injection of 1 per cent etidocaine some distortion and amplitude alterations occurred at the dorsal root entry zone and cauda equina, but the most profound and immediate changes were the marked attenuation of the response evoked by conus medullaris stimulation recorded at the upper thoracic levels, and the responses evoked by sensorimotor cortex stimulation recorded from the conus medullaris (figs. 4 and 7). In all instances, the depression of corticospinal tract activity as shown by the conus medullaris response evoked by sensorimotor cortex stimulation was the most sustained. The slight loss of amplitude and distortion of the conus medullaris response evoked by sciatic nerve stimulation occurred later (45–60 min) than the marked supression of spinal cord white matter transmission.

This information suggests that 1 per cent etidocaine has its most notable effects on the conducting pathways in the dorsal and lateral columns of the spinal cord white matter, and minimal effects on peripheral nerve and the dorsal root entry zone. The onset of flaccid paralysis correlated with the response alterations recorded from the upper spinal cord evoked by conus medullaris stimulation, as well as the response alterations recorded from the conus medullaris evoked by sensorimotor cortex stimulation. Evoked response recovery, however, preceded resolution of the paralysis by 10 to 25 min.

**Discussion**

The peripheral nerve components responsible for the origin of the shock-induced responses employed in this study appear to include a spectrum of high-threshold muscle afferent and cutaneous afferent fibers.11,12 These responses are then conducted into the spinal cord exclusively through the dorsal roots.13,14 At this level, the response is then essentially sensory in nature. At the entrance into the cord, a large-amplitude response is recorded, with a waveform of varying complexity. Such a waveform probably results from the activation of a large interneuronal pool with contributions from the asynchronous discharges of different groups of dorsal horn neurons as the potentials spread along divergent pathways.11,12 In the present study these responses are represented by those recorded from the conus medullaris evoked by sciatic nerve stimulation. These responses, retrieved from recording electrodes at the T12–L1 vertebral level, usually had the waveform characteristics shown in figure 8.

In analyzing the components of this response, the initial notches on the downslope of the main negative wave have been found to follow the dorsal column (DC) response. The next notch on the downslope (DHA) probably represents activity in the terminations of afferent fibers within the gray matter of the dorsal horn.15 The remainder of the negative wave...
(DHI) is acknowledged to represent depolarization of internuncial and relay cells within the dorsal horn,\textsuperscript{15,16} and the slowly rising positive wave (PAD) results from synaptically mediated depolarization of the terminals of incoming afferent fibers.\textsuperscript{17,18}

In this report, we use the term “distortion” to describe the temporal broadening and attenuation of the components of this response. The subsequent cephalad spinal cord transmission of these responses has been shown to be almost entirely dependent upon the functional integrity of the dorsal columns, without significant contributions from other cord structures.\textsuperscript{19,20} And, in the present study, is represented by the upper spinal cord responses evoked by conus medullaris stimulation.

Analysis of the effects of the local anesthetic agents used in this study showed that the major contributing factor in determining the area of evoked response alteration was the individual penetrability of the anesthetic agent into the peripheral nerves, dorsal roots, dorsal root entry zone, and spinal cord white matter. These agents all appeared to have their sites of action on those neural structures located within the subarachnoid space. Although evaluation of the peripheral nerve component of the evoked response conducting pathway by monitoring cauda equina responses evoked by sciatic nerve stimulation does not exclude possible paravertebral block of nerve trunks, the temporal sequence of these response alterations does not support such a hypothesis. The onset of cauda equina response changes following injection of 0.5 per cent bupivacaine or 3 per cent chloroprocaine correlated with dorsal root entry zone alterations, but consistently showed recovery to control while the later responses remained attenuated (figs. 3 and 5).

This series of events suggests that the site of blockade at the peripheral nerve level for these local anesthetics occurs at the cauda equina, where the nerve trunks invested only by endoneurium and perineurium course through the subarachnoid space. The degree and duration of this blockade, which was less than that at the dorsal root entry zone and spinal cord levels, suggests that the cauda equina is not a major site of analgesic blockade (figs. 3–5). Etidocaine in a 1 per cent concentration caused no alteration in the cauda equina response except slight enhancement of the later components of the primary waveform (fig. 5).
Bupivacaine and chloroprocaine, in addition to their actions at the cauda equina level, demonstrated their major influence on the conducting pathways by attenuation and distortion of those responses recorded from the conus medullaris evoked by sciatic nerve stimulation (figs. 2 and 3). Although these response changes with both of these local anesthetics suggest that the most profound and sustained blockade occurs in gray matter of the dorsal horns, bupivacaine also decreased conduction through fiber tracts in the dorsal and lateral columns (figs. 2 and 4). The reductions in conduction were similar in onset, duration, and intensity in these two areas, indicating a symmetrical penetration of spinal cord white matter. The reversion of the response alterations, indicating resolution of the physiologic impairment of the corticospinal tracts, as shown by the return of the conus medullaris responses evoked by sensorimotor cortex stimulation, usually occurred before the animals manifested recovery from their flaccid paralysis. Interestingly, on two occasions during the recovery period, these corticospinal tract responses showed enhancement and hyperactivity. This finding suggests that suppression of motor activity during the later stages of bupivacaine-induced blockade may be partially the result of a blockade of gray matter internuncial fibers from the corticospinal tracts to the anterior horn cells, as well as possible depression of internuncial inhibitory fibers.

Unlike the other local anesthetics examined, etidocaine, 1 per cent, had its predominant response change at the level of the spinal cord white matter, with relative sparing of conduction in the cauda equina and dorsal horn gray matter (figs. 3–5). It is this local anesthetic that, when administered epidurally, appears to fulfill the concept of a "subarachnoid block in disguise." In conjunction with its reduction of dorsal column conduction, the corresponding rapid and sustained attenuation of corticospinal tract responses indicated greater spinal cord white matter penetration than was found with bupivacaine. The relative absence of corresponding dorsal root and root entry zone blockade with 1 per cent etidocaine suggests that some afferent conduction may continue through other ascending spinal cord pathways that cannot be evaluated by use of the present investigational model.

This study supports the concept that local epidural anesthetics have the spinal cord as their major sites of analgesic blockade. Each agent, however, showed rather selective regions of altered electrophysiologic activity within the spinal cord, with only bupivacaine producing significant alterations in both gray and white matter structures (figs. 3, 4). These findings with epidurally injected bupivacaine conform to those spinal cord regions found by Cohen to have the greatest uptake of intrathecally administered "C-labeled lidocaine and procaine. In that study, drug uptake was higher in the gray matter than in the white matter of the cord, and the highest white matter concentrations were found in the dorsal and lateral columns. The other two agents in the present study, however, were more selective in their regional involvement, with 3 per cent chloroprocaine essentially limiting its effects to the dorsal horn gray matter and 1 per cent etidocaine altering conduction in the fiber tracts of the white matter.

The correlation of the various regional neural susceptibilities and the different clinical properties of the local anesthetics chosen for this study indicates that this model is a valuable investigational tool. Plots of evoked potential amplitudes against time are provided to illustrate the temporal effects of the anesthetic agents (figs. 9–5). However, care must be exercised in the interpretation of data in this form. The averaged evoked response as used in this study is the summation of spatially distributed neural elements. Changes in response waveform, indicating changes in the relative contributions from the constituents of the neural substrate, may be as important in the understanding of the effects of local anesthetic agents as the more easily quantifiable modalities of amplitude and latency. It is because of this important qualitative information that illustrations of the characteristic response alterations found during this study are presented (figs. 2, 6, and 7). The model's ability to determine reproducible and selective electrophysiologic changes relative to a specific local anesthetic, however, indicates that it provides a valuable method for evaluating the mechanisms of action of local anesthetic agents.

References

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