

Pupillary Assessment of Sensory Block Level during Combined Epidural/General Anesthesia

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Background: Currently, no reliable method exists to determine the level of sensory block during combined epidural/general anesthesia. However, the pupil dilates markedly in response to noxious electrical stimulation during general anesthesia. Presumably, sensory block produced by epidural anesthesia decreases or obliterates this autonomic response. Accordingly, we tested the hypothesis that pupillary dilation in response to noxious stimulation would predict the level of sensory block achieved during combined epidural/general anesthesia.

Methods: We studied eight volunteers and ten patients during combined epidural/general anesthesia. The volunteers were given an epidural infusion of 2% 2-chloroprocaine while general anesthesia was maintained with 0.8% isoflurane and 60% N₂O. In the patients, an epidural infusion of 0.25% bupivacaine was combined with isoflurane and vecuronium. Noxious electrical stimulation was administered to dermatomal segments in a caudal-to-rostral progression. A twofold increase in pupil size following electrical stimulation was considered the predicted block level in volunteers. In patients, an increase in pupil size exceeding 50% was considered the predicted level. After general anesthesia was discontinued, observers blinded to the pupillary measurements independently determined the actual epidural block level using pain in response to a pinprick as the criterion.

Results: The level predicted by pupillary responses was within two dermatomal segments of the actual level in all the volunteers. The predicted and actual block levels were within two segments in eight of the ten patients and never differed by more than four dermatomes.

Conclusions: We conclude that dilation of the pupil in response to electrical stimulation is an accurate test of the sensory block level during combined epidural/general anesthesia.

(Key words: Anesthesia, techniques: epidural; general. Anesthetics, volatile: isoflurane.)

BENEFICIAL effects of epidural analgesia include blunting of the stress response to surgery¹ and reduction of intraoperative blood loss.² Epidural analgesia often is combined with general anesthesia, especially during prolonged operations. However, a potential disadvantage of this combined method is that the sensory block level usually cannot be determined reliably. Sudden intraoperative hypertension and tachycardia may occur when the block level is lower than expected. Conversely, patients can emerge from general anesthesia with levels sufficiently high to compromise ventilation or prolong recovery markedly. In some cases, the epidural catheter may be positioned improperly at the beginning of anesthesia, making postoperative epidural opioid infusions ineffective.

There currently is no reliable method to determine the level of sensory block during combined epidural/general anesthesia. Although blood pressure and heart rate provide a rough indication of the sensory block level, neither is a reliable predictor because hemodynamic values are altered by a variety of factors, including vascular volume and administered anesthetic agents. Somatosensory evoked potentials are diminished below the sensory level, but the differences above and below the block level are small and difficult to measure.³ Lack of sweating and loss of the sympatho-galvanic response also can be used to detect the level of sympathetic block,⁴ but these tests are technically inconvenient for routine clinical use.

We recently observed that the pupil dilates markedly in response to noxious stimuli during isoflurane anesthesia, whereas the hemodynamic responses are small and unpredictable.⁵ Presumably, sensory block produced by epidural anesthesia decreases or obliterates this pupillary response to pain. Accordingly, we tested the hypothesis that pupillary dilation in response to noxious stimulation would predict the level of sensory block achieved during combined epidural/general anesthesia.

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Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication April 2, 1993. Supported by Augustine Medical, Inc. (Dr. Ozaki is the 1992-1993 Augustine Scholar.) and National Institutes of Health grant GM39723. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, October 1992.

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Methods

With approval of the University of California Committee on Human Research, we studied eight volunteers and ten patients during combined epidural/general anesthesia. All had an American Society Anesthesiologists physical status of 1, and were free of eye disease, taking no medication, and of relatively normal body habitus. The volunteers were evaluated while they participated in a separate thermoregulatory study.⁶

Protocol for Volunteers

Without preanesthetic medication, a catheter was advanced 2–3 cm into the epidural space of eight volunteers. A test dose of 3 ml 2% 2-chloroprocaine HCl (Abbott, North Chicago, IL) with 1:100,000 epinephrine was administered, and was followed in 5 min by slow administration of 15–20 ml 2% 2-chloroprocaine without epinephrine. Subsequently, a continuous infusion of 2% 2-chloroprocaine was administered at a rate of 13–18 ml/h (Program 2 syringe pump; Becton Dickinson, Lincoln Park, NJ). The bolus injection dose and infusion rate were chosen to produce an estimated sensory block level near T10, based on each volunteer's height and age.

General anesthesia was induced by inhalation of 3–4% isoflurane in 70% N₂O and oxygen; thiopental and opioids were not administered. Vecuronium (10 mg) was administered intravenously to facilitate endotracheal intubation. Nitrous oxide was discontinued after induction of general anesthesia and the trachea of each volunteer was intubated.

Anesthesia was maintained with 1.2% isoflurane in oxygen. Ventilation was controlled to maintain end-tidal carbon dioxide tension near 35 mmHg. Airway humidification was provided by placing a Pall Biomedical Products (Glen Cove, NY) heat-and-moisture exchanging filter between the Y-piece of the circle system and the endotracheal tube. Muscle relaxation was maintained by an infusion of vecuronium (Program 2 syringe pump) adjusted to maintain between 0 and 1 twitch in response to supramaximal train-of-four electrical stimulation of the ulnar nerve at the wrist.

Blood pressure, heart rate, hemoglobin oxygen saturation, and gas concentrations were evaluated by monitors incorporated into an Ohmeda Modulus CD anesthesia machine (Madison, WI). Anesthetic data were recorded using IdaCare version 1.3 (Hermes Systems, Angleur, Belgium), which is Macintosh-based (Apple Computer, Cupertino, CA) patient information management software.

The thermoregulatory protocol involved induction of core hypothermia *via* leg cooling, which was accomplished by gradually reducing the temperature of a circulating-water mattress (Blanketrol 11, Maxi-Therm blanket #276, Cincinnati Sub-Zero, Cincinnati, OH) until core temperature reached $36.2 \pm 0.5^\circ \text{C}$. Each volunteer was then rewarmed *via* the legs by gradually increasing the temperature of the circulating-water mattress to 42°C and adding a Bair Hugger forced-air warmer (model 420 lower body cover and model 200 warmer, Augustine Medical, Eden Prairie, MN) set on high. Rewarming was continued until the volunteers once again were normothermic. The cooling and rewarming process required ≈ 4 h. Nitrous oxide (60%) was added to the anesthetic, and the end-tidal isoflurane concentration was adjusted to 0.8%. We chose 0.8% isoflurane because we previously have studied reflex dilation of the pupil at this concentration.⁵ After the end-tidal anesthetic concentrations were stable for at least 3 min, we tested the pupillary response to noxious stimulation.

Electrical stimulation was given with a Neurotec Digistim nerve stimulator (Houston, TX), which delivered a 100-Hz, 60-mA current lasting 5 s. Stimulation started with the left L5 segment and moved cephalad one dermatome segment at a time. The width of each dermatome on the trunk was estimated by measuring the distance between the nipple and the umbilicus and dividing by six. Because thoracic skin above the nipple receives overlapping thoracic and cervical innervation,⁸ the third thoracic dermatome was not tested, and the second thoracic dermatome was tested on the inner aspect of the upper arm. The right side was evaluated similarly.

Pupillary size and light-reactivity were measured before, during, and after the stimulus using a portable infrared pupillometer (Applied Sciences Laboratory, Waltham, MA).⁸ Measurements were taken every 5 s for at least 15 s after each stimulus was presented. If no dilation occurred within 15 s, the stimulating electrodes were moved one dermatome cephalad, and the stimulus presentation was repeated. The first dermatome in which electrical stimulation more than doubled pupil size was considered the predicted sensory block level. Stimulating sequential dermatomes and evaluating pupillary responses required approximately 5 min for each side of the body. Each dermatome was tested only once on each side of the body.

General anesthesia and the vecuronium infusion then were discontinued and neuromuscular paralysis was

reversed by administration of neostigmine (3 mg) and glycopyrolate (0.6 mg). When the volunteers were sufficiently alert, response to pinprick was evaluated by anesthesiologist who was blinded to the results of the pupillary measurements. The first dermatome in which the pinprick produced a sharp sensation was considered the actual block level. The sensory block level was determined separately on each side. When testing was complete, the epidural anesthetic infusion was discontinued.

Protocol for Patients

We studied ten sequential, qualifying patients scheduled for operative procedures appropriate for combined epidural/general anesthesia. Most were undergoing open abdominal procedures. Midazolam (1–2 mg) was administered for sedation, and an epidural catheter was positioned at L4–L5, using standard technique. A test dose of lidocaine (3 ml, 1.5%) and epinephrine (1:200,000) was administered and followed by epidural administration of 10 ml pH-adjusted 2% lidocaine without epinephrine. Five to 7 min later, onset of the block was confirmed by testing for absence of cold discrimination in the groin with an alcohol swab.

General anesthesia was induced by intravenous administration of thiopental (3–5 mg/kg). Vecuronium bromide (0.1 mg/kg) was given to facilitate intubation of the trachea. Up to 15 µg/kg alfentanil was given during the first 15 min of general anesthesia. Esmolol (0.5–1.5 mg/kg) was given as needed to control tachycardia during induction of anesthesia.

General anesthesia was maintained with isoflurane (0.5–1.0%) end-tidal concentration. Muscular paralysis was continued throughout surgery by infusion of vecuronium sufficient to maintain one or two twitches in response to train-of-four stimulation of the ulnar nerve at the wrist. Mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide tension near 35 mmHg. Anesthetic gas concentrations were recorded using a Capnomac II (Datex, Helsinki, Finland).

During the first hour of surgery, pH-adjusted 2% lidocaine without epinephrine was administered *via* the epidural catheter; subsequently, epidural analgesia was maintained by an infusion of 0.25% bupivacaine at 10–15 ml/h. Additional bolus injections of 0.25% bupivacaine (5–10 ml) were administered *via* the epidural catheter when an increase in blood pressure, heart rate, pupillary dilation, or sweating suggested inadequate block. We attempted to avoid bolus injections during

the hour preceding pupillary testing, but one patient was given a bolus 45 min before pupillary testing. Hypotension was treated, when necessary, by intravenous administration of fluids and/or phenylephrine (50–150 µg). Near the end of surgery, the end-tidal concentration of isoflurane was adjusted to 0.8–1.0%. During or shortly after placement of the surgical dressing, the level of sensory block was determined using the pupillary response to noxious stimulation.

The stimulation protocol and pupillary measurements in the patients were similar to those used in the volunteers, but, because of operating room time constraints, we stimulated only the left side and only every other dermatome. Preliminary studies indicated that pupillary size in patients did not consistently double following stimulation, even in areas, such as the face, that could not have been blocked by epidural anesthesia. Therefore, we considered pupillary dilation exceeding 50% to indicate the first unblocked segment in patients.

General anesthesia and the vecuronium infusion then were discontinued and neuromuscular paralysis was reversed by administration of neostigmine (3 mg) and glycopyrolate (0.6 mg). Subsequently, fentanyl (2 µg/kg) or alfentanil (15 µg/kg) was administered as necessary to suppress coughing during extubation of the trachea. The patients were transported to the post anesthesia care unit. When they were sufficiently alert, but before administration of sedative or opioid drugs, the sensory level in response to pinprick was evaluated on the left side by anesthesiologist who was blinded to the results of the pupillary measurements. The first dermatome in which the pinprick produced a sharp sensation was considered the actual block level. At that time, the epidural anesthetic infusion was discontinued.

Data Analysis

Morphometric characteristics of the participants, duration of anesthesia, and core temperature at the time of pupillary testing were compared using two-tailed, unpaired *t*-tests.

The block levels determined by pupillary testing during general anesthesia and the levels subsequently determined by response to pinprick were compared. When a sensory level determined by pupillometry (i.e., predicted levels) was rostral to the actual pinprick level, the difference was assigned a positive value; when the pupillary-predicted level was below the actual pinprick level, a negative value was assigned. The mean

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differences between the predicted and actual block levels were calculated separately in the volunteers and patients. Results are reported as means \pm SD, with $P < 0.05$ identifying statistically significant differences.

Results

Table 1 shows the morphometric characteristics of the study participants, their core temperature values at the time of pupillary testing, and the duration of anesthesia in each group.

Volunteers

Initial pupil sizes at the time of sensory testing were 2.1 ± 0.3 mm. Stimulation of lower lumbar dermatomes did not produce detectable pupillary dilation. As more rostral dermatomes were stimulated, pupillary responses initially remained trivial, but suddenly increased two- to threefold in a single dermatome (fig. 1). Stimulation of the first and second dermatomes below that segment produced only slight pupillary dilation. Stimulation of the dermatome three segments caudal to the active dermatome did not change pupil size (fig. 2).

Because each volunteer was tested bilaterally, there were 16 predictions of the sensory level. The predicted block levels on the left side were within two dermatomal segments of the predicted levels on the right side, except in one volunteer, who had a five-segment difference. The actual block levels also differed by five segments in this individual. The actual block levels for the balance of the study groups averaged $T12 \pm 2$ segments and ranged from T6 to L5. The block level predicted by pupillary response always was within two dermatomes of the actual level subsequently determined by response to pinprick. The predicted and actual dermatomes were the same in six trials. The predicted level was one dermatome rostral to the actual level in six trials, two dermatomes rostral

Table 1. Morphometric Characteristics of the Study Participants, Duration of Anesthesia, and Core Temperature Values

	Volunteers	Patients
Gender (M/F)	2/6	3/7
Age (yr)	28 ± 6	$42 \pm 17^*$
Duration (h)	4.5 ± 1.1	4.9 ± 2.2
Core temperature ($^{\circ}$ C)	36.2 ± 0.5	$34.9 \pm 1.1^*$

* Statistically significant differences between the groups.

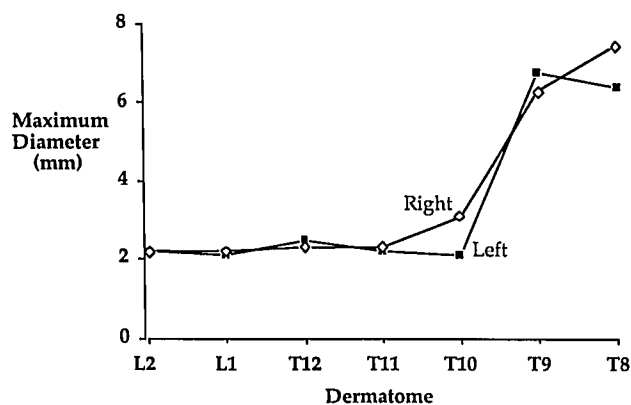


Fig. 1. Maximum pupil size following intense electrical stimulation at dermatomes between L2 and T8 in a typical volunteer. The pinprick level in this volunteer was T10 on the right and left sides.

in two trials, and one dermatome caudal in two trials (fig. 3). Overall, the test was accurate to within 0.5 ± 0.9 dermatomes. Actual block levels were determined 39 ± 21 min after pupillary testing.

Patients

Initial pupil sizes at the time of sensory testing were 1.9 ± 0.5 mm. The actual block levels averaged $T6 \pm 2$ segments, and ranged from T2 to T11. In eight of the ten patients, the block level predicted by pupillary response during general anesthesia was within two segments of the actual level subsequently determined in the post anesthesia care unit; the predicted and actual levels never differed by more than four segments in any patient.

The predicted and actual block levels were the same in two trials. The predicted level was four segments

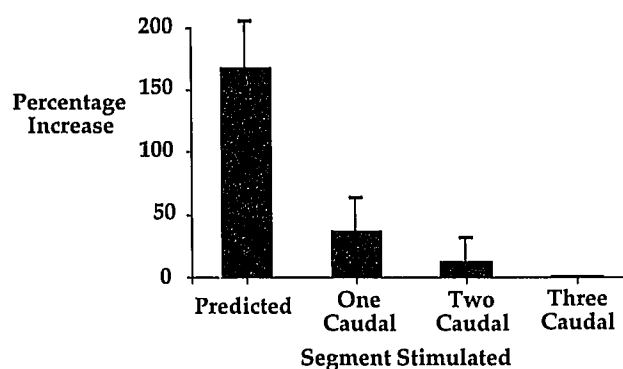


Fig. 2. Noxious electrical stimulation had little effect on pupil size until the predicted segment was reached.

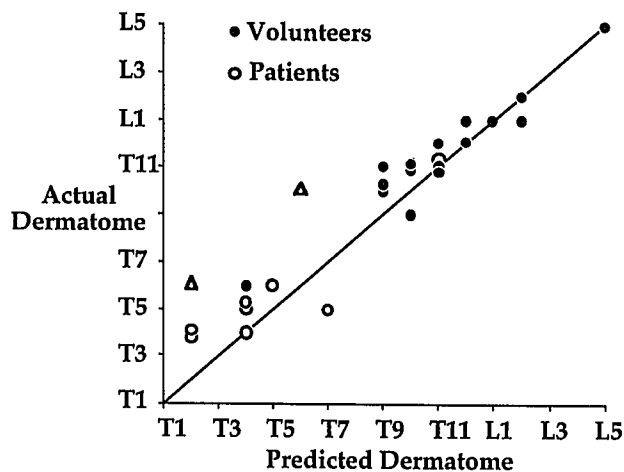


Fig. 3. Correlation between the sensory levels predicted by pupillary testing in anesthetized subjects and the actual pinprick levels determined subsequently when subjects were alert. Data in the volunteers are shown with filled circles; results in the patients are shown with open circles. The two patients in whom the intervals between pupillary and pinprick testing exceeded 100 min are shown with open triangles.

rostral in two trials, two segments rostral in two trials, one segment rostral in three trials, and two segments caudal in one trial (fig. 3). Overall, the test was accurate to within 1.3 ± 1.8 dermatomes. Noxious stimulation two dermatomes caudal to the predicted segment did not significantly increase pupil size. The average increase in pupil size at the predicted dermatome was $123 \pm 44\%$; the smallest increase was 70%.

The interval between the predictive test and the subsequent pinprick test was 50 ± 31 min. In two patients, this interval exceeded 100 min; the predicted level and the actual block level differed by four segments only in these two patients.

Discussion

In most cases, in both volunteers and patients, we were able to predict the level of sensory block to within two dermatomes of the actual block level. We therefore conclude that pupillary dilation in response to electrical stimulation reliably identifies the level of sensory block during combined epidural/general anesthesia. The two patients in whom our predictive test was inaccurate by four segments had an interval between pupillary and pinprick tests that exceeded 100 min. Poor prediction thus may have resulted from a change in the block level following predictive testing.

Initial pupil size in both the volunteers and patients was ≈ 2.0 mm at the time of sensory testing. This value

is consistent with our previous findings.⁵ Although we considered a 50% increase in pupil size as an indication of the first unblocked dermatome in patients, the observed increases always were at least 70% and averaged $\approx 120\%$. Even starting with a pupil diameter of ≈ 2 mm, a 70% increase usually can be detected by simple observation. We thus expect that the level of sensory block can be evaluated reliably in surgical patients without the type of high-resolution scanning pupillometer we used.

We must consider the possibility that the absence of pupillary dilation in response to noxious stimulation primarily indicates block of the sympathetic efferent fibers that originate from the first two thoracic segments and innervate the dilator muscle of the iris. If this were the sole mechanism of dilation and the regional anesthetic obliterated this response, dilation resulting from noxious stimulation from any part of the body would be prevented. However, in each of our participants, there was a zone of demarcation below which pupillary dilation was absent and above which dilation was elicited easily. Furthermore, in some subjects, this zone of demarcation was in the lumbar dermatomes, an area of block unlikely to include the sympathetic fibers innervating the iris. These data, therefore, suggest that sympathetic blockade is not the primary mechanism by which the pupillary response to noxious stimulation is eliminated. Based on experiments with cats and monkeys,⁹ dilation during anesthesia in humans probably results from inhibition of the pupilloconstrictor nucleus by neural impulses within the pain pathway.¹⁰

Although electrical stimulation of the skin activates all fiber types including $A\beta$,¹¹ it is likely that the pupil dilates specifically in response to activation of C or $A\delta$ fibers associated with nociception. The basis for this conclusion is that other types of sensory stimulation, including touch (during pupillary measurements), pressure (due to the automatic blood pressure cuff), and cutaneous cooling, did not produce pupillary dilation. These data suggest that pupillary dilation during general anesthesia is part of a wider autonomic response pattern through which reactions to threatening situations are mobilized. Trivial stimuli such as those of light touch and pressure do not constitute threats and, therefore, are ignored.

If the pupil dilates specifically in response to noxious stimulation during combined epidural/general anesthesia, it should remain small during operations below the level of block. Although we did not test this hypothesis, it would appear to be a useful clinical appli-

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cation of our results. Sensory innervation of the diaphragm originates from the cervical segments of C3–C5.¹² Similarly, vagal afferent nerves may be activated by manipulation of the peritoneum.¹³ Therefore, pupillary dilation resulting from peritoneal stimulation might be difficult or impossible to suppress with epidural anesthesia. Nonetheless, we were able to detect block levels reliably, even though most of our patients underwent intraabdominal surgery. Our testing, however, was not performed during stretching of the peritoneum or irritation of the diaphragm.

The transition from full sensation to total sensory block during epidural anesthesia typically requires several dermatomes. This transition presumably is gradual because each dermatome is innervated by more than one spinal segment.¹⁴ Furthermore, the concentration of local anesthetic at the cephalic border of blocked dermatomes likely is less than that near the injection site. Nonetheless, we were easily able to identify a discrete dermatome in which noxious stimulation resulted in a marked increase in pupil size.

The protocols differed somewhat in volunteers and patients. We did not administer nitrous oxide to the patients because preliminary observations in previously tested patients suggested that this agent slightly blunted pupillary dilation. Nevertheless, the dilation was still less extensive in patients than in volunteers. Three other differences might explain this discrepancy. The patients were an older population, were mildly hypothermic at the time of pupillary testing, and were given a small dose of opioid¹⁵ several hours before the predictive test. Although any of these factors might reduce the pupillary changes, we have not studied formally the effects of age, opioids, or temperature on the extent of pupillary dilation after noxious stimulation. Despite our lack of knowledge concerning these factors, however, we were able to predict the actual level of sensory block in both volunteers and patients.

We used isoflurane at end-tidal concentrations between 0.8% and 1.2% because previously we demonstrated consistent pupillary dilation in response to electrical stimulation in this range.⁵ The response of the pupil to stimulation has not been studied at other concentrations; consequently, we cannot be certain that the level of sensory block could be determined at other isoflurane concentrations.

Administration of droperidol¹⁶ would constrict the pupil and, presumably, reduce pupillary dilation in response to noxious stimulation. The extent to which anesthetic adjuvant drugs might impede application of

our methods remains to be determined. Similarly, certain rare pupillary syndromes reduce iris mobility, presumably preventing this method of sensory level testing. Our study also did not evaluate block levels during spinal anesthesia. However, we expect our method of detecting the level of sensory block to work equally well in patients given general anesthesia and subarachnoid local anesthetics.

In summary, we used dilation of the pupil in response to electrical stimulation of the skin to predict the sensory level during combined epidural/general anesthesia in volunteers and patients. The pupillary response was predictive of the actual level of block with an accuracy within two dermatomes in nearly all trials. Consequently, we conclude that dilation of the pupil in response to electrical stimulation is an accurate test of the level of sensory block during combined epidural/general anesthesia.

The authors would like to thank Ohmeda, Inc. for their loan of a Modulus CD integrated anesthesia machine; Mallinckrodt Anesthesia Products, Inc. for their donation of the thermocouples; Datex Medical Instrumentation, Inc. for their loan of a Capnomac anesthetic gas monitor; Becton Dickinson & Company for their loan of a Program 2 syringe pump; Hermes Systems, Inc. for their loan of an IdaCare automatic record-keeping system; Cincinnati Sub-Zero, Inc. for their loan of a Blanketrol II circulating-water mattress; and Pall Biomedical Products, Inc. for their donation of heat-and-moisture exchanging filters. The authors also thank Winifred von Ehrenburg for her editorial advice.

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