Lidocaine Does Not Depress Reflex Dilation of the Pupil


Background and Objectives. Pupillary dilation in response to dermatomal electrical stimulation is one method of determining sensory block level during combined epidural and general anesthesia. Use of this technique may, however, be confounded by systemic absorption of epidurally administered local anesthetics. Accordingly, the effects of intravenous lidocaine on the magnitude and duration of reflex pupillary dilation were evaluated. Methods. Six volunteers were each anesthetized twice with desflurane 3.5-6.0%. During one anesthetic, intravenous lidocaine was administered to a plasma concentration of 5.3 ± 1.5 µg/mL. When the plasma concentrations were stable, a 5-second tetanic electrical stimulus was applied. Pupil size was then recorded for 8 minutes. Results. Lidocaine, at plasma concentrations near 5 µg/mL, did not significantly alter the pupillary response to electrical stimulation. In contrast, stimulus-induced increase in heart rate was obliterated. Painful stimulation did not increase systolic blood pressure in either case. Conclusions. Typical plasma lidocaine concentrations observed during epidural anesthesia are unlikely to prevent the use of pupillary responses to evaluate sensory block level. Reg. Anesth 1997: 22: 461--465.

Key words: pupil size, reflex dilation, desflurane lidocaine.

Neuraxial block is often combined with general anesthesia. One difficulty associated with this method is that general anesthesia makes determination of sensory block height difficult. Because of inaccuracies in estimates based on hemodynamic measurements, block levels sometimes prove to be higher or lower than desired. One method of quantifying sensory block level during combined regional and general anesthesia depends on dilation of the pupil in response to dermatomal electrical stimulation (1). Determination of block level using dilation of the pupil in response to a noxious stimulus proved reliable with 2-chloroprocaine or bupivacaine epidural anesthesia (1). However, systemic absorption of other local anesthetics—particularly lidocaine—can be substantial. For example, plasma concentrations of lidocaine during epidural anesthesia often approach 5 µg/mL. (2). This dose has significant systemic effects including analgesia, slurred speech, circumoral numbness, and light-headedness (3-5). Similarly, bolus injections of lidocaine reduce hemodynamic responsiveness (6). Because most analgesic and sedative drugs blunt autonomic reflexes and reduce pupillary activ-
ity (7), plasma lidocaine concentrations such as those observed during epidural anesthesia might impair pupillary dilation in response to electrical stimulation, thereby preventing accurate determination of block level. Accordingly, we tested the hypothesis that plasma lidocaine concentrations typically observed during epidural anesthesia prevent adequate pupillary dilation in response to electrical stimulation.

**Methods**

With Committee on Human Research approval and informed consent, we studied six male volunteers. All were young, healthy, free of eye disease, and were not taking any medications. Morphometric characteristics of the volunteers included: age, 29 ± 6 years; weight, 72 ± 6 kg; and height, 178 ± 6 cm.

**Treatment Protocol**

Six volunteers were each anesthetized twice, with at least 2 days elapsing between each session. General anesthesia was induced by intravenous injection of propofol (=2 mg/kg) and maintained with desflurane. Following neuromuscular relaxation with 0.1 mg/kg vecuronium bromide, the trachea was intubated and end-tidal desflurane concentration was adjusted to 3.5%. Because stimulation produced slight head movements in the first three subjects (which complicated but did not prevent pupillary measurement), the next three patients were given 6% end-tidal desflurane. Ventilation was controlled to maintain end-tidal PCO$_2$ 35-40 mm Hg.

After 15 minutes of equilibration, we started a 23-minute masked infusion of either lidocaine or saline placebo, in a randomly assigned order. On returning for the second anesthetic, the volunteer was given the same amount of desflurane as during the first anesthetic, but was given the alternate (saline or lidocaine) intravenous agent. Lidocaine was infused by a computer-controlled pump that targeted a total plasma lidocaine of 5 μg/mL, using the pharmacokinetic data of Tucker and Mather (8). After 15 minutes of drug infusion, a 60-70 mA, 100-Hz, 5-second noxious electrical stimulus (Digistim 2, Houston, TX) was administered to the T9 dermatome via silver/silver chloride surface electrodes. Venous blood samples for lidocaine determinations were obtained before the infusions were started and then immediately before and 8 minutes after administration of the tetanic stimulus. Plasma samples were stored at −20°C until analysis.

**Measurements**

Routine anesthetic monitors were used in all cases. Oscillometric blood pressure and heart rate were evaluated before and every minute after stimulation with a Dinamap TM 1846 SX (Critikon Inc., Tampa, FL). End-tidal gas concentrations were determined by a Capnomac II (Datex Medical Instrumentation, Inc., Tewksbury, MA). Core temperature was measured in the distal esophagus using an esophageal stethoscope (Mon-a-Therm, St. Louis, MO).

Pupil size was measured immediately before, during (elapsed time zero), and at 0.25, 0.5, 1, 1.5, 2, 2.5, 4, and 8 minutes after noxious stimulation using a portable infrared pupillometer (Fairville Medical Optics Inc., Amersham, England). This method of pupillary measurement has been previously described (9). Electrical stimulation was designated elapsed time zero: Earlier times were considered “prestimulus” and subsequent times were considered “poststimulus.”

Bound and unbound plasma lidocaine concentrations were evaluated using high-pressure liquid chromatography. The unbound fraction was isolated by equilibrium dialysis. The lidocaine assay that was used is linear to at least 100 μg/mL with a detection limit of 0.01 μg/mL (0.05 μg/mL for ultrafiltrate) with a 200-μL injection and within-day coefficient of variation of 3.9% (n = 6) at 5 μg/mL.

**Statistical Analysis**

Prestimulus and poststimulus values were compared using two-tailed, paired t-tests. Anesthetic management, pupillary responses, and hemodynamic responses during each infusion were also compared using two-tailed, paired t-tests. As suggested by Matthews et al., statistical analysis was restricted to curve descriptors (10). These descriptors included maximum heart rate and blood pressure, maximum pupillary response magnitude, and time to maximum response. Results are presented as mean ± SD; P < .05 was considered statistically significant.

**Results**

Pupillary and hemodynamic responses were virtually identical in the volunteers given 3.5 and 6% desflurane. Consequently, results in the six volunteers were combined. Patients were slightly hypothermic, but core temperature was comparable during each treatment (Table 1). Total plasma
Table 1. Pupillary and Hemodynamic Responses

<table>
<thead>
<tr>
<th>Target [Lidocaine] (μg/mL)</th>
<th>0</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Lidocaine] (μg/mL)</td>
<td>—</td>
<td>5.3 ± 1.7</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>35.4 ± 0.3</td>
<td>35.6 ± 0.4</td>
</tr>
<tr>
<td>[Desflurane] (%)</td>
<td>4.8 ± 1.4</td>
<td>4.75 ± 1.4</td>
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Preinfusion | Pupil size (mm) | 2.4 ± 0.3 | 2.3 ± 0.3 |

Prestimulus | Pupil size (mm) | 2.2 ± 0.6 | 2.4 ± 0.3 |
| Max systolic blood pressure (mm Hg) | 114 ± 14 | 109 ± 6   |
| Max heart rate (beats/min)          | 68 ± 5   | 63 ± 6    |

Poststimulus | Max pupil size (mm) | 5.6 ± 1.9* | 5.6 ± 1.7* |
| Time to max size (min)              | 1.3 ± 0.5 | 1.6 ± 1.3  |
| Time to return (min)                | 5.6 ± 2.8 | 6.2 ± 2.9  |
| Max systolic blood pressure (mm Hg) | 119 ± 17  | 115 ± 12   |
| Max heart rate (beats/min)          | 78 ± 14*  | 65 ± 10    |

* Statistically significant differences between prestimulus and poststimulus values. Time to return is defined by recovery to within 10% of prestimulus size. Results are presented as mean ± SD. Responses did not differ significantly at the two target lidocaine concentrations.

Lidocaine concentrations at the time of stimulation averaged 5.3 ± 1.5 μg/mL (range, 3.9–7.7 μg/mL), with an unbound fraction of 1.4 ± 0.3 μg/mL (range, 1.0–2.0 μg/mL) (Table 1). Lidocaine concentrations increased in three volunteers and decreased in these volunteers in the 8 minutes following stimulation. These changes were small (.48 ± .55 μg/mL) and thus the values before and 8 minutes after stimulation did not differ significantly.

Following electrical stimulation on the control day, pupil size increased 254 ± 29%. Dilations ranged from 0.4 to 5.5 mm. Pupil size increased comparably during lidocaine administration (Fig. 1). Electrical stimulation produced pupillary dilation, exceeding 2 mm in five of the six volunteers, with or without lidocaine. The dilation in one volunteer was considerably smaller: 0.5 mm (1.7–2.3 mm) during saline infusion and 0.4 mm (2.2–2.6 mm) during lidocaine infusion. Heart rate increased 9 ± 3% (P < .05) during saline administration, but remained nearly constant when lidocaine was given (Fig. 2). Systolic blood pressure

![Fig. 1. Pupillary dilation in response to electrical stimulation (at elapsed time zero) did not differ significantly with and without lidocaine. The background anesthetic was desflurane, 4.8 ± 1.4%. Total plasma lidocaine concentrations at the time of stimulation averaged 5.3 ± 1.5 μg/mL, with an unbound fraction of 1.4 ± 0.3 μg/mL. Results are presented as mean ± SD. See Table 1 for statistical analysis.](image1)

![Fig. 2. Lidocaine (5.3 ± 1.5 μg/mL plasma concentration) abolished the increase in heart rate induced by noxious electrical stimulation (at elapsed time zero) during desflurane anesthesia (4.8 ± 1.4% end-tidal concentration). Results are presented as mean ± SD. See Table 1 for statistical analysis.](image2)
remained unchanged during both saline and lidocaine infusions (Fig. 3).

Discussion

Plasma concentrations of lidocaine during epidural anesthesia generally increase in proportion to the dose and the duration of the anesthetic (2), frequently reaching concentrations near 5 μg/mL—a level causing various symptoms (4,5) and analgesia (3) in unanesthetized humans. Our results indicate that lidocaine concentrations near 5 μg/mL did not significantly alter pupillary responses to noxious stimulation. It is thus unlikely that typical plasma lidocaine concentrations would interfere with pupillometric determination of the sensory block level during combined epidural and desflurane anesthesia. Our results are therefore similar to the findings of Klasen et al. who showed that intravenous lidocaine had no effect on the somatosensory evoked potentials after stimulation of the posterior tibial nerve, whereas epidural lidocaine significantly prolonged latency (11).

The analgesic effects of systemic lidocaine have been recognized for many years but the mechanisms involved remain poorly understood. Some authors have suggested that lidocaine attenuates neuropathic pain caused by deafferentation, but not pain of peripheral origin such as tourniquet pain (3). Lidocaine reduces the response of primary afferent fibers to formalin, but not to electrically evoked activity (12). Similarly, it reduces spinal sensitization induced by C-fiber stimulation (13). Lidocaine is also known to reduce adrenergic transmission and to relax smooth muscle by a direct action on the muscle (14,15). Consequently, hemodynamic alterations induced by noxious stimulation such as laryngoscopy and intubation are suppressed by intravenous lidocaine administration (6). Because lidocaine obliterated the tachycardia induced by noxious stimulation, our results support a depressant effect of lidocaine on adrenergic responsiveness. The trend toward lower heart rate and blood pressure during lidocaine infusion is consistent with decreased sympathetic tone. Reflex pupillary dilation during desflurane anesthesia is not a sympathetic reflex (16) and, perhaps for this reason, was unaltered by intravenous lidocaine administration.

Electrical stimulation was administered via surface electrodes, whereas needles were used in our previous studies (9,16). The ideal stimulus to provide maximum pupillary dilation is unknown. Stimulus frequency (17), duration of the stimulus, and maximum current are presumably important factors. Neither surface electrodes (18) nor needle electrodes (19) consistently provide supramaximal stimulation, particularly when repeated and frequent stimulations are administered (20). We have found, however, that surface electrodes are more convenient for the determination of block levels during general anesthesia. Surface electrodes are less cumbersome than needle electrodes and eliminate the risks of inadvertent needle sticks. With this method of stimulation, we observed brisk dilations in five volunteers, but a dilation of only 0.4–0.5 mm in the sixth. Although this small dilation would be difficult to detect visually, it was easily quantified with infrared pupillometry. Administration of higher currents, a feature available from some commercially available stimulators (i.e., Fisher-Paykel, Auckland, New Zealand), might consistently elicit large pupillary dilations.

As in our previous studies, blood pressure and heart rate were inconsistent indicators of noxious stimulation (9). Blood pressure did not increase significantly after stimulation in either the saline- or lidocaine-treated volunteers. This finding contrasts with previous studies that demonstrated small, but significant, increases in blood pressure following stimulation. The difference is presumably due to the comparatively weak stimulus provided by surface electrodes in this study.

One shortcoming of this study was the use of 3.5% end-tidal desflurane in three volunteers and 6% end-tidal desflurane in three others. However, each volunteer received the same concentration of
desflurane for each portion of the study (saline vs lidocaine). Other studies have shown that there is only a small difference in the maximum pupillary responses to noxious stimulation at high and low concentrations of desflurane (16). Furthermore, the responses were virtually identical at each anesthetic concentration. We thus believe that combining data obtained at the two concentrations was appropriate.

In summary, pupillary dilation in response to noxious stimulation is an established method of determining sensory block level during combined epidural and general anesthesia. We evaluated the effects of intravenous lidocaine on the magnitude and duration of reflex pupillary dilation. At plasma concentrations near 5 \( \mu \text{g/mL} \), lidocaine did not significantly alter the pupillary response to electrical stimulation during desflurane anesthesia. Typical plasma lidocaine concentrations observed during epidural anesthesia are thus unlikely to prevent using pupillary responses to evaluate sensory block level.

**References**