Alfentanil Blocks Reflex Pupillary Dilation in Response to Noxious Stimulation But Does Not Diminish the Light Reflex

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Background: Estimation of the μ-agonist opioid effect in anesthetized and paralyzed patients is often imprecise and can be obscured by concomitant administration of drugs that affect the sympathetic nervous system, such as β-adrenergic blocking agents. As an alternative to hemodynamic measures of opioid effect, the authors tested the hypothesis that the pupillary light reflex or pupillary reflex dilation correlated with alfentanil concentrations during isoflurane anesthesia.

Methods: Six volunteers were anesthetized on 4 days with 0.8% isoflurane. Alfentanil was administered intravenously to target total plasma concentrations of 0, 25, 50, and 100 ng/ml. A 5-s tetanic electrical stimulus was applied to the skin. Pupil size and the pupillary light reflex were recorded before and after alfentanil administration, and before and for 8 min after the stimulus.

Results: Alfentanil exponentially impaired reflex pupillary dilation, decreasing the maximum response amplitude from 5 mm at 0 ng/ml to 2.3 mm at 25 ng/ml to 1.0 mm at 50 ng/ml and finally to 0.2 mm at 100 ng/ml. In contrast, only the highest concentration of alfentanil depressed the dilation of the pupil in the first 2 s after the stimulus. Alfentanil administration had no effect on the pupillary light reflex.

Conclusions: Dilation of the pupil in response to a noxious stimulus is a measure of opioid effect in isoflurane-anesthetized volunteers. In contrast, the pupillary light reflex is unaffected by alfentanil during isoflurane anesthesia. These data suggest that stimulus-induced pupillary dilation may be used to evaluate the analgesic component of a combined volatile and opioid anesthetic. (Key words: Anesthetics, volatile; isoflurane. Anesthetic technique: epidural. Opioids: alfentanil. Pupil: size; reflex dilation.)

SURGICAL trauma produces well-defined hormonal and metabolic responses, primarily by activating midbrain and hypothalamic centers that control autonomic function. Based on Crile's original theories, an anesthetic is incomplete unless it contains both hypnotic and analgesic components that are designed to limit this stress response. Although volatile anesthetics often fail to eliminate the stress response to surgery, it can be markedly attenuated by supplements including epidural analgesia and intravenous opioids.

Measuring the efficacy of these analgesic supplements in anesthetized and paralyzed patients is often imprecise. Analgesia may be inferred when the hemodynamic response to surgery is attenuated. However, circulatory responses can be altered by a host of unrelated factors, including vasoactive drugs, β-adrenergic blockade, and vascular volume shifts.

We recently showed that pupillary dilation in response to noxious stimulation during anesthesia is not
a spinal sympathetic reflex. Pupillary dilation after stimulation implies activity of central pathways as high as the rostral mesencephalon, where the pupilloconstrictor nucleus is located. This dilation is not depressed by β-adrenergic blockade or by high concentrations of volatile anesthetics. In contrast, epidural analgesia, which fails to fully block somatosensory-evoked potentials, obliterates reflex dilation of the pupil during isoflurane anesthesia.

Thus we wondered whether another analgesic, alfentanil, would also attenuate pupillary reflex dilation during isoflurane anesthesia. We also wanted to determine how well attenuation of the pupillary responses to noxious stimulation would compare with the attenuation of hemodynamic responses. Our hypothesis was that alfentanil would attenuate reflex dilation in a dose-dependent manner and correlate better with opioid effect than heart rate and blood pressure. Volatile anesthetics depress the light reflex. However, the effect of opioids on the human pupillary light reflex during anesthesia has been curiously unexplored. Therefore, we simultaneously measured the effect of alfentanil on the small residual light reflex that remained during isoflurane anesthesia.

Methods

With approval of the University of California, San Francisco, Committee on Human Research and written informed consent, we studied six male volunteers. Their age was 28 ± 6 (mean ± SD) yr, weight was 70 ± 9 kg, and height was 177 ± 7 cm. All were young, healthy, free of eye disease, and taking no medications.

Treatment Protocol

Six volunteers each participated on four different study days, separated by at least 48 h. On each occasion, anesthesia was induced with propofol (2 mg/ml) and maintained with isoflurane via a laryngeal mask. After a separate thermoregulatory study lasting 4 ± 1 h, vecuronium bromide was administered, and the trachea was intubated. The end-tidal isoflurane concentration was adjusted to 0.8% and ventilation was controlled to maintain end-tidal partial pressure of carbon dioxide (PETO2) at 35–40 mmHg.

After at least 15 min, a blinded computer-controlled infusion of alfentanil or saline placebo was started to randomly assigned target plasma concentrations of 0, 25, 50, or 100 ng/ml. Alfentanil was administered using a computer-controlled syringe pump (Ohmeda 9000; Ohmeda, Steeton, UK). The infusion profile was based on plasma efflux, with coefficients estimated from published pharmacokinetic data. A targeted alfentanil infusion lasting 15 min should exceed by several minutes the time for equilibration between plasma and site-effect concentrations.

After at least 15 min of drug or saline infusion, a 60- to 70-MA, 100-Hz, 5-s noxious electrical stimulus (Digitim 2, NeuroTechnology, Houston, TX) was administered to the T-9 dermatome via steel needle electrodes. Venous samples to determine total plasma alfentanil concentration were obtained before the infusion was started and before and 8 min 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 using a Dinamap 1846 SX (Critikon, Tampa, FL). End-tidal gas concentrations were determined using a Capnomac II (Datex Medical Instrumentation, Tewksbury, MA). Core temperature was measured in the distal esophagus (Mon-a-Therm, Mallinckrodt, St. Louis, MO).

Pupil size, light reflex, and reflex dilation were measured using a portable infrared pupillometer (Fairville Medical Optics, Amersham, UK). This device displays the pupil on a liquid crystal display as a void in the center of an area of infrared light reflected from the iris. At the release of a button, the infrared scan begins with a flash of visible light (130 candelas/m²). Individual pupillary diameters during anesthesia can vary as much as 0.2 mm, presumably because of noise within the pupillometer system or hand movement. When two or three scans are averaged, as is usual, the light reflex can be measured to within 0.05 mm, which is the resolution of the instrument. The pupillometer we used was controlled by an external laptop computer. A newer version integrates all required electronics into the hand-piece of the instrument.

For the current study, we measured pupil size and light reflex amplitude before the start of the alfentanil infusion and then immediately before, during (elapsed time zero), and 0.25, 0.5, 1, 2, 2.5, 4, and 8 min after noxious stimulation. We covered the measured right eye with a rubber cup to exclude ambient light and taped the left eye closed. Scans lasted 2 s, and the light stimulus was 0.2 s. Except for the scan taken at elapsed
time zero, we recorded two or three scans and used the averaged scan for each measurement.

For each alfentanil infusion rate, we compared maximum constriction velocity and light reflex amplitude for the averaged scans before the infusion was started, with the averaged scan taken just before the noxious stimulus. We also measured the difference between the starting diameter and the final diameter 2 s after the start of the stimulus (fig. 1). This difference was taken as a measure of the early dilation (dilation at 2 s) of the pupil at each alfentanil plasma concentration.

Total plasma alfentanil concentrations were determined by high-performance liquid chromatography, using a modification of a previously described technique. This assay is linear to at least 10,000 ng/ml, with a detection limit of 2 ng/ml, and within-day coefficient of variation of 4.1% (n = 6) at 250 ng/ml.17

Statistical Analysis

Alfentanil concentrations, core temperatures, isoflurane concentrations, pupillary measures (light reflex amplitude, constriction velocity, and dilation in the first 2 s), heart rates, and systolic blood pressures at each alfentanil target concentration were compared using repeated-measures analysis of variance and Scheffé’s F tests.

Maximum poststimulus values of heart rate, systolic blood pressure, pupillary light reflex, and pupil size were compared with the prestimulus values using two-tailed, paired t tests. As suggested by Matthews et al.18 statistical analysis was restricted to curve descriptors.

Based on inspection of the data, the relation between plasma alfentanil concentration and stimulus-evoked change in pupillary size was fit to an exponential equation. Results are presented as mean ± SD; P < 0.05 was considered significant.

Results

According to the protocol, plasma alfentanil concentrations at the time of stimulation on each of the study days differed significantly but were near the target concentrations (table 1). Typical responses are illustrated in figure 1. Alfentanil concentrations did not change significantly in the 8 min after stimulation. Alfentanil infusion did not alter prestimulus pupil size (tables 1 and 2).

Alfentanil impaired reflex pupillary dilation, decreasing the response amplitude from 5 mm at 0 ng/ml, to 2.3 mm at 25 ng/ml, to 1.0 mm at 50 ng/ml, and finally to 0.2 mm at 100 ng/ml (fig. 2). The relation between plasma alfentanil and the poststimulus change in pupil size measured in millimeters was exponentially related to total plasma alfentanil concentration in nanograms per milliliter: size = 4 e0.0327[Alfentanil]; r² = 0.78. Pupillary dilation thus was 50% inhibited at a plasma alfentanil concentration of only about 20 ng/ml. In contrast, the correlation between plasma alfentanil concentration and the change in heart rate or systolic blood pressure was relatively poor (fig. 3). Alfentanil administration also markedly reduced the time required for pupil size to return to baseline values. For example, a plasma alfentanil concentration of 25 ng/ml decreased recovery time from 7.6 min to 2.3 min (table 1).

Dilation of the pupil during the first 2 s of noxious electrical stimulation was only slightly decreased, even by the highest alfentanil concentration. Light reflex amplitude and maximum constriction velocity were not significantly altered at any alfentanil concentration (table 2, fig. 4). Power analysis indicated that we had a greater than 80% chance of detecting a difference in the light reflex of 0.05 mm and in the maximum constriction velocity of 0.25 mm/s.

Discussion

Volatile and intravenous anesthetics are often combined with opioids because it is widely appreciated that synergy between these drug classes permits administration of lower doses of each, and consequently reduced overall toxicity. Often a standard dose of each drug is given, and adjustments are made in reaction to hemodynamic changes that occur during the operation. One difficulty with this approach, however, is that variability in individual responsiveness may result in excessive or inadequate administration of either drug type. Thus we sought a more precise measure of opioid effect during isoflurane anesthesia.

Alfentanil produced a substantial dose-dependent depression of pupillary dilation after a noxious stimulus; dilation was reduced to 50% of control values at alfentanil concentrations near 20 ng/ml, and was nearly abolished at concentrations approaching 100 ng/ml. Although we could not directly measure pain in these anesthetized, paralyzed volunteers, opioids produce analgesia and there was a good correlation between plasma alfentanil concentration and magnitude of reflex dilation. Pupillary dilation correlated better with alfend...
Table 1. Pupillary Size, Blood Pressure, and Heart Rate After Stimulation at Each Alfentanil Concentration

<table>
<thead>
<tr>
<th></th>
<th>Target [Alfentanil] (ng/ml)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>[Alfentanil] (ng/ml)</td>
<td>—</td>
<td>22 ± 2.7</td>
<td>47 ± 9.8</td>
<td>94 ± 20</td>
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<tr>
<td>Core temperature (°C)</td>
<td>35.1 ± 0.5</td>
<td>35.2 ± 0.4</td>
<td>35.0 ± 0.7</td>
<td>35.0 ± 0.6</td>
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<tr>
<td>Isoflurane (%)</td>
<td>0.79 ± 0.01</td>
<td>0.80 ± 0.04</td>
<td>0.79 ± 0.05</td>
<td>0.8 ± 0.03</td>
</tr>
<tr>
<td>Preinfusion</td>
<td>Pupil size (mm)</td>
<td>2.3 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Prestimulus</td>
<td>Pupil size (mm)</td>
<td>2.3 ± 0.1</td>
<td>2.3 ± 0.2</td>
<td>2.2 ± 0.2</td>
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<tr>
<td></td>
<td>Maximum systolic BP (mmHg)</td>
<td>109 ± 6</td>
<td>103 ± 5</td>
<td>107 ± 9</td>
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<td></td>
<td>Maximum HR (beats/min)</td>
<td>64 ± 11</td>
<td>61 ± 7</td>
<td>56 ± 10</td>
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<tr>
<td>Poststimulus</td>
<td>Maximum pupil size (mm)</td>
<td>7.3 ± 0.9^{2,4}</td>
<td>4.6 ± 1.3^{5,4}</td>
<td>3.2 ± 0.7^{1}</td>
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<td></td>
<td>Time to maximum size (min)</td>
<td>1.3 ± 0.8</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.3</td>
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<td></td>
<td>Time to return (min)</td>
<td>7.6 ± 1.8^{2,4}</td>
<td>2.3 ± 1.3^{5,4}</td>
<td>1.1 ± 0.8^{1}</td>
</tr>
<tr>
<td></td>
<td>Maximum systolic BP (mmHg)</td>
<td>124 ± 9^{6}</td>
<td>120 ± 16</td>
<td>111 ± 7</td>
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<td></td>
<td>Maximum HR (beats/min)</td>
<td>73 ± 13^{6}</td>
<td>73 ± 13</td>
<td>76 ± 9</td>
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During the "Preinfusion" period, volunteers were anesthetized with isoflurane. "Prestimulus" indicates the period when isoflurane anesthesia was combined with alfentanil administration. The "Poststimulus" period was after supra-maximal cutaneous electrical stimulation. "Time to return" defined by recovery to within 10% of pre-stimulus size. Results are mean ± SD. Per protocol alfentanil plasma levels were statistically significant different on the three dose days.

*t = Statistically significant differences between prestimulus and poststimulus values are indicated by 1 = significantly different from control; 2 = significantly different from 25 ng; 3 = significantly different from 50 ng; 4 = significantly different from 100 ng.

Fig. 1. The light reflex is defined by the difference between the initial diameter and the minimum diameter after a short light stimulus. Maximum constriction velocity is the maximum speed (measured in millimeters per second) attained during the constriction phase of the light reflex. Reflex dilation is the difference between the initial diameter and the diameter at the end of a 2 s scan. The data shown are the mean scans taken before and after alfentanil administration (25 ng/ml). See table 1 for the statistical analysis.

Our finding that alfentanil had no effect on the light reflex, but essentially blocked reflex dilation, was unexpected. In unanesthetized persons, Pickworth et al. showed that buprenorphine, morphine, heroin, codeine, oxycodone, and hydrocodone all depressed both the magnitude of the light reflex and maximum constriction velocity. The studies of Pickworth et al. were confounded by simultaneous drug-induced changes in pupillary size. Pupillary constriction reduces the mechanical range available for iris movement. Further, the optical stimulus for constriction is reduced because retinal light flux decreases as the pupil becomes mitotic. Our study, in contrast, was performed in anesthetized persons whose pupils were consistently mitotic and did not change size after opioid administration. Under these circumstances, the pupillary light reflex was well maintained after alfentanil administration. Our findings are consistent with a previous study that found no effect of bolus injections of fentanyl on the light reflex during the stable miosis of desflurane anesthesia.
Table 2. The Pupillary Light Reflex and Early Dilation at Each Alfentanil Concentration

<table>
<thead>
<tr>
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<th>Target (ng/ml)</th>
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<tr>
<td></td>
<td>0</td>
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<tr>
<td>Preinfusion Light</td>
<td>0.24 ± 0.1</td>
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<tr>
<td>reflex (mm)</td>
<td></td>
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<tr>
<td>Maximum constriction</td>
<td>−1.3 ± 0.1</td>
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<tr>
<td>velocity (mm/s)</td>
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<tr>
<td>Prestimulus Light</td>
<td>0.24 ± 0.10</td>
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<tr>
<td>reflex (mm)</td>
<td></td>
</tr>
<tr>
<td>Maximum constriction</td>
<td>−1.2 ± 0.3</td>
</tr>
<tr>
<td>velocity (mm/s)</td>
<td></td>
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<tr>
<td>During stimulus</td>
<td>0.37 ± 0.09</td>
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<tr>
<td>Dilation in 2 s (mm)</td>
<td></td>
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<tr>
<td>Poststimulus Maximum</td>
<td>0.80 ± 0.26&lt;sup&gt;3,4&lt;/sup&gt;</td>
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<tr>
<td>light reflex (mm)</td>
<td></td>
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</tbody>
</table>

Values are mean ± SD.

* Statistically significant differences between prestimulus and poststimulus values. 1 = significantly different from control; 3 = significantly different from 50 ng; 4 = significantly different from 100 ng.

We targeted alfentanil concentrations known to have respiratory and analgesic effects. Substantial respiratory depression is produced by alfentanil concentration of only 108 ng/ml, and 100 ng/ml provides adequate postoperative analgesia for most patients. Alfentanil at these concentrations also has significant effects during isoflurane anesthesia. An alfentanil concentration of only 29 ng/ml reduces the minimum alveolar concentration (MAC) of isoflurane by 50%; 100 ng/ml reduces this value by approximately 70%. The volunteers who received our largest alfentanil dose (100 ng/ml) were also receiving 0.8% isoflurane. This end-tidal concentration, combined with 100 ng/ml alfentanil, is reported to be approximately twice that concentration required to prevent movement in 50% of patients after a painful stimulus (2 MAC). That we failed to detect opioid-induced depression of the light reflex, even with a sensitive electronic pupillometer, suggests that the light reflex is well preserved at typical clinical doses of alfentanil.

The effects of alfentanil and the volatile anesthetics on pupillary reflexes thus differ significantly. For example, increasing end-tidal isoflurane concentration from 0.7 MAC to 1.0 MAC decreases the light reflex by about 50% without any significant change in pupil size. Although there is considerable interindividual variability in the magnitude of the light reflex at any given end-tidal concentration, regression analysis indicates that the light reflex is usually absent at concentrations exceeding 1.5 MAC. Reflex dilation, in contrast, is not diminished as isoflurane concentration is increased from 0.7 MAC to 1.0 MAC or desflurane is increased from 0.6 MAC to 1.1 MAC. Presumably a higher concentration could be attained in which all transmission through the spinal cord would fail, but such concentrations would rarely be required in clinical practice.

We tested only a single background isoflurane concentration (0.8%). Although we have previously shown that the pupillary response to noxious stimulation is similar at 0.8% and 1.2% end-tidal isoflurane, it is not known what effect other isoflurane concentrations might have on opioid-induced depression of reflex dilation. It is likely that alfentanil will prove less effective in reducing reflex dilation at lower isoflurane concentrations. We
also studied only young men. The elderly are more sensitive to opioids, and women respond somewhat differently than men do to certain opioid agonists. Reflex pupillary dilation might, therefore, be abolished at different alfentanil concentrations in the elderly or in women. We also anticipate that persons who are tolerant to opioids would be resistant to suppression of reflex dilation by opioid agonists. Our study followed a separate thermoregulatory study during which isoflurane was administered for about 4 h and core temperatures were manipulated. Although it seems unlikely, results may differ in persons given shorter anesthetics.

Opioids produce a dose-dependent attenuation of reflex dilation in response to noxious stimulation. In contrast, the pupillary light reflex is unaffected by alfentanil during isoflurane anesthesia. These data suggest that stimulus-induced pupillary dilation may be used to evaluate the analgesic component of a combined volatile and opioid anesthetic.

References

5. George JM, Reier CE, Lanese RR, Rower MJ: Morphine anesthe-
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sia blocks cortisol and growth hormone response to surgical stress in humans. J Clin Endocrinol Metab 1974; 38:736-41
27. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987; 240:159-65