Autonomic effects of epidural and intravenous fentanyl

M. D. Larson1*, P. D. Berry2, J. May1, A. Bjorksten3 and D. I. Sessler4

1Department of Anesthesia and Perioperative Care, University of California, San Francisco, USA. 2Royal Free Hospital, Pond Street, London NW3 2QG, UK. 3Department of Anaesthesia, Royal Melbourne Hospital, Parkville, Victoria, Australia. 4Department of Outcomes Research, The Cleveland Clinic, Outcomes Research Institute, University of Louisville, KY, USA

*Corresponding author: Department of Anesthesia and Perioperative Care, University of California, Box 0648, San Francisco 94143-0648, CA, USA. E-mail: larsonm@anesthesia.ucsf.edu

Background. We tested the hypothesis that there is greater suppression of autonomic reflexes during general anaesthesia when fentanyl is administered epidurally than when it is given intravenously.

Methods. Ten volunteers were anaesthetized with desflurane. Noxious stimuli of variable intensity were then delivered by tetanic electrical stimuli. Heart rate, arterial pressure, and pupillary dilation in response to these stimuli defined nociception. Seven of these volunteers participated twice using a crossover design: they received i.v. fentanyl on one study day and epidurally on the other. Autonomic responses to alternative tetanic stimuli at L4 and C5 dermatomes were measured every 5 min for 3 h after fentanyl administration.

Results. After a brief redistribution period, plasma fentanyl concentrations were virtually identical on both days. After stimulation of the L4 dermatome only, block of pupillary reflex dilation was greater by 47 (22)% after epidural fentanyl compared with i.v. fentanyl. Time to maximal depression of reflex dilation after L4 stimulation was 41 (13) min. Arterial pressure and heart rate decreased after fentanyl by either route but there were no differences observed between L4 and C5 stimulations.

Conclusion. We conclude that during general anaesthesia, epidural fentanyl enhances antinociception by a spinal mechanism which can be detected by pupillary dilation but not by changes in arterial pressure or heart rate.


Keywords: anaesthetic techniques, epidural; analgesics, opioids, fentanyl; pain; parasympathetic nervous system; pupils, pupillary reflex dilation; sympathetic nervous system

Accepted for publication: October 27, 2006

Opioids are often given during general anaesthesia to control autonomic reflexes. Well-known postoperative side-effects of opioids include respiratory depression, nausea, and sedation. Additionally, opioids cause acute tolerance and opioid-induced hyperalgesia.1 2 Because of concerns about side-effects, anaesthesiologists now try to restrict perioperative opioid administration.3 4 One way to reduce the total dose is to inject the opioids in the epidural space. Bolus injections of epidural fentanyl, for example, are known to enhance analgesia in unanaesthetized subjects compared with the same dose given intravenously.5–8

Spinal opioid receptors that suppress nociception from lumbar dermatomes lie in the spinal cord segments below the lower thoracic epidural space.9 10 We thus asked whether these opioid receptors could be activated by administration of epidural fentanyl during desflurane anaesthesia. If epidural fentanyl does suppress autonomic reflexes to a greater extent than i.v. fentanyl, this might be a method to reduce the total opioid dose during surgical procedures in which an epidural catheter is in place.

Accordingly, we studied anaesthetized volunteers to test the hypothesis that epidural administration of fentanyl deposited in the lower thoracic epidural space would suppress autonomic measures of nociception more than the same dose administered intravenously, that this
suppression of autonomic responsiveness would be a seg-
mental effect, and that it would mimic the effect caused
by decreasing the intensity of the stimulus.

Methods
We designed the following study to compare the effects of
i.v. fentanyl to epidural fentanyl during general anaes-
thesia. We measured heart rate and arterial pressure after
noxious stimulation and observed suppression of these
responses after administration of epidural or i.v. fentanyl.
Infrared pupillometry was added as an additional measure
of autonomic function because pupillary reflex dilation
(PRD) is a sensitive measure of nociception during
general anaesthesia.11 12 If deposition of fentanyl in the
lower thoracic epidural space does enhance analgesia at a
lower lumbar dermatome compared with i.v. adminis-
tration, it should have the same effect on autonomic
nervous system responses as that obtained by decreasing
the intensity of the noxious stimulus. Specifically, the pre-
viously described shape of PRD13 should be altered in a
similar manner by these two interventions because they
would both decrease stimulus-evoked activity in the sec-
ondary neuron of the nociceptive pathway.

With ethical and procedural approval from the
Committee on Human Research at the University of
California at San Francisco, the Research Advisory Panel of
the State of California, and written informed consent from
each volunteer, we studied 10 ASA I volunteers, some of
whom simultaneously participated in a previously published
study.13 Exclusion criteria included BMI
2
35 yr.
ors of eye or neurological disease, contraindication to
epidural analgesia, medications other than oral
contraceptives, and age <18 or >35 yr.

Using a randomized crossover design, volunteers
consented to participate on 2 days separated by at least
48 h. The volunteers were given general anaesthesia and
fentanyl on both study days. However, fentanyl was given
intravenously on one study day and epidurally on the
other. Treatment order was randomly assigned.

On the epidural study day, a catheter was inserted via the
T10–T11 interspace using standard technique. No premed-
ication or test dose was given. On both study days, general
anaesthesia was induced with propofol (3 mg kg
−1) and
ecuronium bromide (0.15 mg kg
−1); the trachea was intu-
bated, and the lungs mechanically ventilated to maintain
end-tidal carbon dioxide near 4.6 kPa. Anaesthesia was
maintained with desflurane 5% end-tidal in oxygen 50%
and nitrogen 50%. Lactated Ringer’s solution was given at
approximately 3 ml kg
−1 h
−1 through a catheter in the left
arm. Vecuronium was infused to provide one-to-two me-
chanical twitches in response to supra-maximal electrical
stimulation of the ulnar nerve at the wrist.

PRD was induced by noxious electrical stimulation at
two sites: the L4 and C5 dermatomes. The L4 dermatome,
the distal site, is located on the medial aspect of the right
leg. Nerve fibres from the L4 dermatome enter the spinal
cord between the thoracic spines of T10 and T12,14 so we
assumed that enhanced antinociception, if any, would
apply to this site. The C5 dermatome, the proximal site, is
located on the lateral aspect of the right shoulder. To
stimulate the dermatomes, stainless steel needle electrodes
(1.5 cm long) were inserted subcutaneously 3 cm apart at
each site. Stimulation started 30 min after induction of
anaesthesia and continued for 180 min after i.v. or
epidural fentanyl administration. Each site was stimulated
for 3 s with a 100 Hz electric current (Digistim II,
Neurotechnology, Dallas, TX, USA). The two sites were
stimulated alternately, with 5 min separating each stimulus.
The initial stimulation site was assigned randomly.

Before fentanyl was given, the electrical stimulation
was adjusted to deliver variable intensities of stimulation.
We categorized stimulation intensities into two categories,
a low intensity stimulus (20–70 mA) and a high intensity
stimulus (50–90 mA). A post hoc analysis suggested that
the difference between the peak and end diameters (P–E
diameters) would quantitate the altered shape of PRD
produced by high and low intensity currents.

After this period of variable intensity stimulation, but
before fentanyl administration, the stimulation current was
set to approximately 65 mA and then adjusted slightly, as
necessary, to provide equal pupillary dilations from the C5
and L4 sites.

After baseline pupillary measurements (see below),
fentanyl (3 μg kg
−1 diluted in 10 ml of saline) was given
i.v. or epidurally, as randomly designated, in a 5 min
period. After a 3 h measurement period, nalozone 400 μg
was administered i.v. within 5 min. Ten minutes after the
start of nalozone administration, two more measurements
were taken, one from each stimulation site. Following
these measurements, the neuromuscular block was antago-
nized and anaesthesia discontinued.

Approximately 1 h after emergence from anaesthesia
on the epidural study day, lidocaine 20%, 10 ml was
injected into the epidural catheter in a 5 min period.
The extent of the sensory block was subsequently eval-
uated by sensory response to pinprick after 10, 15, and
20 min, and the maximum extent of the block was
recorded.

Core temperatures were monitored in the distal
oesophagus (Tyco-Mallinckrodt Anesthesiology Products,
St Louis, MO, USA), and body temperature was kept near
37°C with active surface warming. Venous arterial
blood for fentanyl analysis was sampled from the right
arm before and 5, 10, 15, 30, 60, 90, 120, and 180 min
after i.v. or epidural fentanyl was given. Plasma
specimens were frozen at −20°C for subsequent gas
chromatographic analysis.15 The limit of detection was
near 0.2 ng ml
−1.

Pupillary responses were measured with an infrared
pupillometer (Fairville Medical Optics, Buckinghamshire,
UK), programmed to scan the pupil at the rate of 20 Hz for 10 s from the start of the tetanic electric stimulus. PRD was quantified by integrating the area above the baseline pupil size for each entire 10 s scan. We have previously described this methodology and used it to quantify opioid effect. Ambient light was maintained near 150 lux, and the contralateral eye was covered during measurements.

Systolic and diastolic arterial pressures were measured oscillometrically (Dinamap TM 1846 SX; Critikon Inc., Tampa, FL, USA) 2 to 3 min after each stimulus. Heart rate and oxyhaemoglobin saturation were monitored continuously using three-lead electrocardiography and a Nellcor N200 pulse oximeter (Hayward, CA, USA), respectively. Resting heart rate and arterial pressure were recorded prior to the start of stimulations (‘before stimulation’). Heart rate and arterial pressure after stimulations were the highest values recorded after each stimulus and before the next stimulus. End-tidal desflurane and end-tidal carbon dioxide were monitored continuously (infrared analyzer, Datex, Finland).

Data analysis
Depression of PRD, heart rate, and systolic arterial pressure for the 3 h study period were each expressed as the AAC as determined by the trapezoid rule and comparisons were made using paired tests. For all $P < 0.05$, 95% confidence intervals were calculated.

To analyse the effects of i.v. and epidural fentanyl on the shape of PRD, we calculated the average of all 18 measurements at each stimulation site. We then calculated the peak-minus-end diameters (P–E diameter) as previously described and compared these values on the epidural and i.v. study days at both stimulation sites using paired $t$-tests. We also used two-tailed paired $t$-tests to compare peak depressant effect and time-to-peak effect between the epidural and i.v. study days.

Analysis of variance was used to compare ‘before stimulation’ values to ‘before fentanyl’ values and also to compare ‘peak effect’ values to ‘before fentanyl’ values. All data are reported as mean (sd) unless otherwise indicated; $P < 0.05$ was considered statistically significant.

Results
Participants were 27 (5) yr old, weighed 69 (8) kg, and were 176 (11) cm tall. There were six men and four women. Of the 10 volunteers participating on the first study day, three did not return for the second study day. In one subject, the epidural produced a unilateral block following lidocaine 2%; this volunteer returned for a second epidural study day and results from this second day were used in our analysis. Paired data on fentanyl administration were, therefore, collected from the seven volunteers who completed both arms of the study.

PRD in response to low- and high-intensity stimulating currents was obtained from all 10 volunteers before fentanyl administration. The PRD (Fig. 1, Table 1) was smaller in response to the low-intensity stimulus, predominately because the late phase of PRD was depressed (Fig. 1, Table 1). Changes in heart rate, but not arterial pressure, were significantly smaller in response to the lower current (Table 1).

Stimulating currents were between 60 and 70 mA before fentanyl and did not differ between the two study days or between the L4 and C5 stimulation sites (Table 2). Before fentanyl administration, pupillary responses were similar after noxious stimulation at the L4 and C5 dermatomes (Table 2) on both the i.v. and epidural study days. P–E diameter did not differ before fentanyl administration (Table 2).

Plasma fentanyl concentrations were initially three-fold greater in the i.v. group; but within 15 min, plasma concentrations after epidural and i.v. administration were comparable and remained so for the rest of the measurement period (Fig. 2).

The 3 h reduction of PRD (AAC) was greater after L4 stimulation on the epidural study day than on the i.v. study day (Table 2, Fig. 3). In contrast, the suppression of PRD after C5 stimulation was similar with both i.v. and epidural administration of fentanyl (Table 2, Fig. 3). Fentanyl administration decreased heart rate and blood pressure by both routes of administration (Fig. 4, Table 3). No differences were observed in arterial pressure or heart rate between the epidural and i.v. study days and no segmental effects were noted (Fig. 4, Table 3).

The curves representing PRD following epidural and i.v. fentanyl diverged after 50 min with L4 stimulations (Fig. 3), but these curves did not diverge after C5
stimulations (Fig. 3). Time to maximum effect was longer after epidural administration than after i.v. administration at both stimulation sites for PRD reduction, heart rate, and arterial pressure (Tables 2 and 3).

An unusual pupillary response was observed following stimulation of the L4 dermatome after epidural injection: there was an increased depression of PRD at L4 produced by a late reduction of the reflex that was not apparent on the scans following i.v. fentanyl (Fig. 5). This was statistically confirmed by comparing the effect of the two methods of fentanyl administration on the P–E diameters (Table 2). The similarity between this altered PRD reflex shape to that observed after a decrease in the intensity of the noxious stimulus was readily apparent (compare Figs 1 and 5). The change in the shape of the PRD curve and the decrease in PRD after epidural administration at L4 were both reversed by naloxone (Table 2).

### Discussion

The autonomic effects of epidural fentanyl in anaesthetized human subjects remain poorly characterized, but are nonetheless important because these measures are often used to gauge nociception during anaesthesia. Ours is the first study to measure the common autonomic responses

![Fig 2](image-url) Serum fentanyl concentrations after bolus injection of 3 μg kg⁻¹ of either i.v. (black squares) or epidural (black triangles) fentanyl. Results presented as mean (sd).

![Fig 3](image-url) Changes in PRD (mm s) after epidural or i.v. fentanyl. C5 stimulations (A) and L4 stimulations (B). Error bars are s.e.m. Statistical analysis (AAC) is presented in Table 2.
Autonomic effects of epidural fentanyl

Fig 4 Changes in heart rate after fentanyl following stimulation of the C5 dermatome (A) or L4 dermatome (B) on epidural and i.v. study days. Error bars are SEMs. Statistical analysis (AAC) is presented in Table 3.

Table 3 Blood pressure and heart rate before and after stimulation and before and after i.v. or epidural fentanyl. AAC, area above the curve. P-values refer to i.v. vs epidural comparisons of same dermatome. *P < 0.05 compared with ‘before stimulus’ values. **P < 0.05 compared with ‘before fentanyl’ values. Results presented as means (SD). If P < 0.05, data are also presented as effect size [95% confidence intervals].

<table>
<thead>
<tr>
<th>L4</th>
<th>Epidural</th>
<th>I.V.</th>
<th>P-value</th>
<th>Effect size</th>
<th>C5</th>
<th>Epidural</th>
<th>I.V.</th>
<th>P-value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before stimulation</td>
<td>62 (8)</td>
<td>58 (4)</td>
<td>0.20</td>
<td></td>
<td>62 (8)</td>
<td>58 (4)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before fentanyl (after stimulation)</td>
<td>71 (6) *</td>
<td>65 (3)*</td>
<td>0.10</td>
<td></td>
<td>73 (8)*</td>
<td>67 (5)*</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to max change after fentanyl</td>
<td>40 (12)</td>
<td>9 (5)</td>
<td>0.001</td>
<td>31 [25–37]</td>
<td>34 (12)</td>
<td>14 (5)</td>
<td>0.002</td>
<td>20 [14–40]</td>
<td></td>
</tr>
<tr>
<td>At max change after fentanyl (%)</td>
<td>62 (15)**</td>
<td>54 (17)**</td>
<td>0.04</td>
<td>8 [–3 to 19]</td>
<td>61 (17)**</td>
<td>54 (19)**</td>
<td>0.01</td>
<td>7 [–6 to 20]</td>
<td></td>
</tr>
<tr>
<td>AAC (bpm min)</td>
<td>1675 (1109)</td>
<td>1519 (902)</td>
<td>0.40</td>
<td></td>
<td>1429 (1376)</td>
<td>1100 (1198)</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before stimulation</td>
<td>88 (11)</td>
<td>91 (8)</td>
<td>0.10</td>
<td></td>
<td>88 (11)</td>
<td>91 (8)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before fentanyl (after stimulation)</td>
<td>96 (14) *</td>
<td>98 (6)*</td>
<td>0.50</td>
<td></td>
<td>97 (15)*</td>
<td>99 (10)*</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to max change after fentanyl</td>
<td>29 (12)</td>
<td>12 (8)</td>
<td>0.03</td>
<td>17 [10–24]</td>
<td>39 (26)</td>
<td>21 (13)</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At max change after fentanyl</td>
<td>88 (8)**</td>
<td>86 (13)**</td>
<td>0.50</td>
<td></td>
<td>90 (7)**</td>
<td>88 (11)**</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAC (mm Hg min)</td>
<td>1121 (751)</td>
<td>1603 (1163)</td>
<td>0.23</td>
<td></td>
<td>656 (833)</td>
<td>830 (1559)</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Following nociceptive stimuli before and after bolus injections of epidural fentanyl in anaesthetized subjects and to compare the maximum effect and time course of action of epidural fentanyl with i.v. fentanyl.

Epidural fentanyl suppressed PRD 47 (22)% more than i.v. fentanyl over the 3 h study period. This enhanced effect was not caused by higher serum fentanyl concentrations on the epidural study day and it was a segmental effect, observed only at the L4 stimulation site. We thus confirmed our hypothesis that bolus injections of epidural fentanyl have a segmentally enhanced effect on nociception similar to that observed in awake subjects. Our results are in agreement with Inagaki and colleagues 18 who demonstrated a greater reduction of halothane MAC with epidural compared with i.v. fentanyl and with Harakuni and colleagues 19 who demonstrated less hormonal change during gastrectomy with epidural fentanyl.

We confirmed the spinal effect of epidural fentanyl by showing that this route of drug administration produced the same alteration in the shape of PRD as that brought about by decreasing the intensity of the stimulus. The mechanism of PRD is thought to be brought about through activation of a putative inhibitory neuron acting on the pupilloconstrictor nucleus.20 Because the initial phase of the dilation was minimally affected, it appears that the primary alteration brought about by decreasing the intensity of the stimulus, and by epidural fentanyl, is to shorten the duration and not the initial frequency of the neuronal spike train. Similar findings have been observed in the prefrontal cortex where the encoding of nociceptive stimulus intensity is related to spike train duration and not initial firing frequency.21

Fentanyl decreased heart rate and arterial pressure after either i.v. or epidural administration. There was no advantage to either injection method in suppressing these autonomic responses. Additionally, we did not find any segmental differences or any trends which would suggest that a larger sample size would show a segmental effect of epidural fentanyl on heart rate or arterial pressure.

The haemodynamic reflexes that we observed were small compared with PRD and this may account for our inability to detect advantages to epidural administration using arterial pressure and heart rate as our measurement tool. Other studies have also demonstrated greater sensitivity of PRD as a measure of nociception compared with circulatory reflexes.11 12 Possibly, a stronger stimulus, a larger sample size, analysis of heart rate variability, or invasive monitoring would have allowed us to demonstrate a segmental advantage of epidural compared with i.v. fentanyl by using haemodynamic data as our outcome measures.

On the other hand, heart rate and arterial pressure may not be a precise measure of nociception during anaesthesia. One study that used haemodynamic reflexes as a measure of nociception specifically concluded that there was no advantage to administration of epidural compared with i.v. fentanyl.22 Differences in the central mechanisms of pupillary and circulatory reflexes might explain these discrepancies. Whereas heart rate and arterial pressure responses to noxious stimulation are spinal or lower brain
In summary, using pupillometry as a measure of autonomic nerve activity, we have shown enhanced segmental analgesia at a low lumbar dermatome following deposition of epidural fentanyl in the thoracic epidural space. We were unable to detect this difference when using haemodynamic responses as a measure of nociception. The enhanced analgesia effect of epidural fentanyl was not apparent until the second hour after administration, it was more intense than after i.v. fentanyl administration and dissipated within 3 h.

Acknowledgements

Supported by NIH Grant GM 061655 (Bethesda, MD), the Gheens Foundation (Louisville, KY), the Joseph Drown Foundation (Los Angeles, CA), and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY). The study sponsors were not involved in the design of the study, the collection, analysis, or interpretation of the data, or the preparation of the manuscript. None of the authors has a personal financial interest in this research.

References

1 Li X, Angst MS, Clark JD. Opioid-induced hyperalgesia and incisional pain. Anesth Analg 2001; 93: 204–9
4 Kehlet H. Postoperative opioid sparing to hasten recovery: what are the issues? Anesthesiology 2005; 102: 1083–5
12 Constant I, Nghe MC, Boudet L, Berniere J, Schrayer S, Seeman R, Murat I. Reflex pupillary dilatation in response to skin incision and alfentanil in children anaesthetized with
sevoflurane: a more sensitive measure of noxious stimulation than the commonly used variables. Br J Anaesth 2006; 96: 614–9


17 Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. Anesthesiology 1997; 87: 849–55


22 Guinard JP, Carpenter RL, Chassot PG. Epidural and intravenous fentanyl produce equivalent effects during major surgery. Anesthesiology 1995; 82: 377–82


