Opioids Inhibit Febrile Responses in Humans, Whereas Epidural Analgesia Does Not

An Explanation for Hyperthermia during Epidural Analgesia

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Background: Epidural analgesia is frequently associated with hyperthermia during labor and in the postoperative period. The conventional assumption is that hyperthermia is *caused* by the technique, although no convincing mechanism has been proposed. However, pain in the "control" patients is inevitably treated with opioids, which themselves attenuate fever. Fever associated with infection or tissue injury may then be suppressed by opioids in the "control" patients while being expressed normally in patients given epidural analgesia. The authors therefore tested the hypothesis that fever in humans is manifested normally during epidural analgesia, but is suppressed by low-dose intravenous opioid.

Methods: The authors studied eight volunteers, each on four study days. Fever was induced each day by 150 IU/g intravenous interleukin 2. Volunteers were randomly assigned to: (1) a control day when no opioid or epidural analgesia was given; (2) epidural analgesia using ropivacaine alone; (3) epidural analgesia using ropivacaine in combination with 2 μg/ml fentanyl; or (4) intravenous fentanyl at a target plasma concentration of 2.5 ng/ml.

Results: Fentanyl halved the febrile response to pyrogen, decreasing integrated core temperature from 7.0 ± 3.2°C · h on the control day, to 3.8 ± 3.0°C · h on the intravenous fentanyl day. In contrast, epidural ropivacaine and epidural ropivacaine–fentanyl did not inhibit fever. The fraction of core-temperature measurements that exceeded 38°C was halved by intravenous fentanyl, and the fraction exceeding 38.5°C was reduced more than fivefold.

Conclusions: These data support the authors' proposed mechanism for hyperthermia during epidural analgesia. Fever during epidural analgesia should thus not be considered a complication of the anesthetic technique *per se*.

HYPERTHERMIA frequently complicates epidural analgesia for labor and delivery[1–4] and after surgery in patients who are not pregnant.[5] A clinical consequence of this hyperthermia is that women given epidural analgesia are more often given antibiotics than in those treated conventionally, and their offspring are more commonly treated for sepsis.[2,6,7] However, a convincing cause for hyperthermia in association with epidural analgesia has yet to be proposed.

Implicit in all discussions of hyperthermia associated with epidural analgesia is the assumption that the technique *causes* hyperthermia.[8] It is important, however, to recognize that the "control" patients in these observational studies were not given a placebo. Instead, their pain was usually treated with opioids. This is a critical factor, because even low concentrations of intravenous opioids attenuate fever.[9] It thus seems likely that fever associated with infection, tissue injury, atelectasis, and so forth is suppressed by opioids in the "control patients," whereas it is expressed normally in patients given epidural analgesia.

We therefore tested the hypothesis that fever in humans is manifested normally during ropivacaine epidural analgesia, but suppressed by low doses of the intravenous opioid fentanyl. Because fentanyl may also be given epidurally, we also evaluated the effects of combined ropivacaine–fentanyl epidural analgesia. Fever is mediated by peripheral release of endogenous pyrogens[10] such as the cytokines interleukin (IL) 6 or tumor necrosis factor (TNF) α. To identify a potential peripheral mechanism by which epidural analgesia may inhibit fever, we therefore simultaneously measured plasma cytokine concentrations.

Patients and Methods

With approval from the University of California, San Francisco, Committee of Human Research and informed

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consent, we studied eight healthy male volunteers, each on four study days. None was obese, was taking medication, or had a history of thyroid disease or Raynaud syndrome. Morphometric and demographic characteristics included: age, 27 ± 6 yr; height, 180 ± 8 cm; weight, 74 ± 8 kg; and body fat, $17 \pm 5\%$.

The volunteers fasted for 8 h before arriving at the laboratory. They were minimally clothed and reclined on a standard operation table during the study. Ambient temperature was maintained near 22°C and relative humidity near 45%. To avoid circadian fluctuations, studies were scheduled at the same time each day.

An 18-gauge catheter was inserted in a left forearm vein for fluid and drug administration. Lactated Ringer's solution at ambient temperature was infused at a rate of 100 ml/h. A 16-gauge catheter was inserted in the right median-cephalic vein for blood sampling.

Protocol

On each study day, the volunteers were randomly assigned to either: (1) a control day when no opioid or epidural analgesia was given; (2) epidural analgesia using 0.2% ropivacaine alone; (3) epidural analgesia using 0.2% ropivacaine in combination with 2.0 μg/ml fentanyl; or (4) intravenous fentanyl at a target plasma concentration of 2.5 ng/ml. Volunteers were then given an intravenous injection of 50 IU/g of human recombinant IL-2 (elapsed time, 0), observed 2 h later by 100 IU/g of the drug (Chiron, Inc., Berkeley, CA). At least 2 weeks were allowed between the fentanyl day and the combined epidural ropivacaine–fentanyl day to minimize tolerance.

On the epidural days, a catheter was inserted into the epidural space *via* the L2–L3 interspace. The epidural catheter was then injected with 2 ml lidocaine, 2%, with epinephrine 1:100,000. This test dose was followed in 5 min by 10–12 ml of 0.2% ropivacaine (Ropivacaine HCl; Astra, Inc., Westborough, MA) or ropivacaine in combination with 2 μg/ml fentanyl without epinephrine. The initial anesthetic dose was based on the volunteers' heights and calculated to produce a dermatomal level of sensory blockade near T8–S1 bilaterally as determined by loss of cutaneous cold sensation and response to pinprick. Epidural analgesia was then maintained with the continuously administered drug at a rate of 8–12 ml/h to maintain the target sensory block level.

On the intravenous fentanyl day, fentanyl was administered using a pump (Ohmeda 9000; Ohmeda, Steeton, UK) programmed to target fentanyl blood concentrations of 2.5 ng/ml using a modification of the Kruger–Thiemer method[11] and published data.[12] This is a low concentration that produces only mild sedation and is similar to concentrations that may be used for labor or postoperative pain.[13,14] To maintain an appropriate end-tidal carbon dioxide tension (P_{CO_2}), the volunteers were reminded to breathe during fentanyl administration, and,

if necessary, oxygen was given *via* nasal cannula to maintain oxygen saturation measured by pulse oximetry (Sp_{O_2}) more than 95%. Fentanyl was infused for 8 h and then discontinued.

Measurements

Core temperature was measured at the tympanic membrane using Mon-a-Therm thermocouples (Mallinckrodt Anesthesiology Product, Inc., St. Louis, MO). Mean skin-surface temperature was calculated from measurements at 15 area-weighted sites.[15] Temperatures were recorded at every 5 min from thermocouples connected to Iso-Thermex thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments Corp., Columbus, OH).

Pupillary responses were measured to evaluate the pharmacodynamic effect of fentanyl. An infrared pupillometer (Fairville Medical Optics, Buckinghamshire, UK) was programmed to provide a 0.5-s, 130 candela/m² pulse of green light and to scan the pupil at the rate of 10 Hz for 2 s from the beginning of the light stimulus. We have previously described this method[16] and used it to quantify opioid effect.[17] The maximum reduction in pupil size during the 2-s scan identified the reflex amplitude. Ambient light was maintained near 150 lux, and the contralateral eye was covered during measurements.

Peripheral venous blood for fentanyl analysis was sampled just before IL-2 administration and at 1, 3, 5, and 7 elapsed h. The plasma samples were stored at −20°C until analysis by gas chromatography, using techniques described by Bjorkman and Stanski[18] and Selinger *et al.*[19] The limit of detection is near 0.2 ng/ml.

We evaluated IL-6, IL-8, and TNF α, as well as the antiinflammatory cytokine IL-10 hourly.[20–23] Plasma IL-6 and IL-8 concentrations were measured by an enzyme-linked immunosorbent assay (Human interleukin-6 and interleukin-8 ELISA Kits; Toray Industries, Inc., Tokyo, Japan). TNF α concentrations were determined by a human immunoassay (Quantikine HS; R&D Systems, Minneapolis, MN). Plasma IL-10 concentrations were determined by a solid-phase enzyme-amplified immunoassay (IL-10 EASIA Kit; Medgenix Diagnostics S.A., Fleurus, Belgium). In each case, the assays were performed *per* the manufacturers' directions, and appropriate calibration curves were constructed. All are highly specific and sensitive over the range of observed values.

Heart rates and arterial oxygen saturation were monitored continuously using pulse oximetry (Biox 3700; Ohmeda, Salt Lake City, UT). Blood pressure at the ankle was determined oscillometrically (Critikon, Tampa, FL). End-tidal carbon dioxide concentrations and respiratory rates were monitored using a Capnomac Ultima (Datex Medical Instruments, Tewksbury, MA). All temperatures and hemodynamic data were recorded at 5-min intervals.

Table 1. Plasma Fentanyl Concentration and Pupillary Responses

	Elapsed Time (h)				
	0	1	3	5	7
Control					
Pupil size (mm)	5.7 ± 0.8	5.6 ± 0.6	6.0 ± 0.6	5.9 ± 0.9	5.5 ± 1.2
Reflex amplitude (mm)	2 ± 0.4	2.2 ± 0.5	2.2 ± 0.3	2.2 ± 0.5	2.2 ± 0.7
Epidural ropivacaine					
Pupil size (mm)	5.8 ± 1.0	5.5 ± 0.7	5.7 ± 1.1	5.8 ± 1.0	6.0 ± 1.0
Reflex amplitude (mm)	2.0 ± 0.5	1.9 ± 0.3	2.1 ± 0.6	2.5 ± 0.9	2.2 ± 0.4
Epidural ropivacaine and fentanyl					
[Fentanyl] (ng/ml)	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.3	0.2 ± 0.2
Pupil size (mm)	5.6 ± 0.7	5.7 ± 0.5	5.3 ± 0.7	5.0 ± 1.0	5.2 ± 1.3
Reflex amplitude (mm)	1.9 ± 0.4	2.0 ± 0.4	1.9 ± 0.5	2.2 ± 0.4	2.0 ± 0.5
Intravenous fentanyl					
[Fentanyl] (ng/ml)	1.1 ± 1.2	1.8 ± 0.8	1.4 ± 0.4	1.5 ± 0.3	1.5 ± 0.4
Pupil size (mm)	5.8 ± 0.8	3.2 ± 0.8*	3.0 ± 0.9*	3.1 ± 0.7*	2.9 ± 0.7*
Reflex amplitude (mm)	2.0 ± 0.4	1.2 ± 0.7*	1.1 ± 0.5*	1.1 ± 0.4*	1.1 ± 0.5*

* Statistically significant differences from elapsed time 0. Pupil sizes during intravenous fentanyl administration all differed significantly from the other treatment days.

Data Analysis

Febrile responses on each study day are presented as time-dependent changes. Specifically, we considered integrated core temperature, peak temperature, and the time-to-peak temperature. Values were integrated during 3–8 elapsed h, with respect to the mean temperature during the first elapsed hour. That is, we calculated the area under the temperature curve. This quantified the extent to which core temperature exceeded initial values (in °C · h) and is a standard way of expressing fever magnitude.

Ambient temperature and humidity, hemodynamic responses, end-tidal P_{CO_2}, respiratory rate, Sp_{O_2}, and administered fluid volume on each study day were first averaged within each volunteer during 3–8 elapsed h; the resulting values were then averaged among volunteers.

Most results were compared using repeated-measures analysis of variance and Scheffé F test. Time-dependent changes were similarly evaluated. A chi-square analysis was used to evaluate the fraction of the temperature measurements in each group exceeding 38.0, 38.5, and 39.0°C. Results are presented as mean ± SD; $P < 0.05$ was considered statistically significant.

Results

The volunteers were only mildly sedated by intravenous fentanyl. Total plasma fentanyl concentrations during administration of fentanyl averaged 1.5 ± 0.2 ng/ml on the intravenous fentanyl day, but only 0.2 ± 0.1 ng/ml when fentanyl was given epidurally. Pupil size and reflex amplitude were significantly reduced by intravenous fentanyl (table 1). There were no significant differences in ambient temperature, relative humidity, heart rate, blood pressure, end-tidal P_{CO_2}, and Sp_{O_2} on the four study days.

Table 2. Environmental, Hemodynamic, Respiratory, and Thermoregulatory Data

	Control	Epidural Ropivacaine	Epidural Ropivacaine and Fentanyl	Intravenous Fentanyl
Ambient temperature (°C)	21.9 ± 0.7	21.7 ± 0.2	21.7 ± 0.4	21.4 ± 0.4
Relative humidity (%)	47 ± 5	48 ± 5	47 ± 4	48 ± 3
Initial core temperature (°C)	36.6 ± 0.2	36.6 ± 0.2	36.6 ± 0.2	36.7 ± 0.3
Mean arterial blood pressure (mmHg)	88 ± 9	79 ± 8	80 ± 10	89 ± 11
Heart rate (beats/min)	92 ± 12	90 ± 13	87 ± 13	92 ± 13
End-tidal P_{CO_2} (mmHg)	37 ± 4	33 ± 9*	35 ± 8	43 ± 4
Administered fluid volume (l)	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Maximum core temperature (°C)	38.7 ± 0.6*	38.7 ± 0.7*	38.7 ± 0.9*	38.1 ± 0.7
Time to maximum core temperature (h)	6.1 ± 1.0	6.6 ± 0.9*	6.6 ± 0.6*	5.8 ± 0.9
Integrated core temperature (°C · h)	7.0 ± 3.2*	7.0 ± 3.3*	6.0 ± 3.8*	3.8 ± 3.0
Mean skin temperature (°C)	34.9 ± 0.5*	35.3 ± 0.7*	34.7 ± 0.8	33.8 ± 1.1

All values were averaged or integrated over 3–8 elapsed hours, corresponding to the period of epidural analgesia or intravenous fentanyl administration. Data are presented as mean ± SD.

* Statistically significant differences from intravenous fentanyl. There were no significant differences among the other treatment groups.

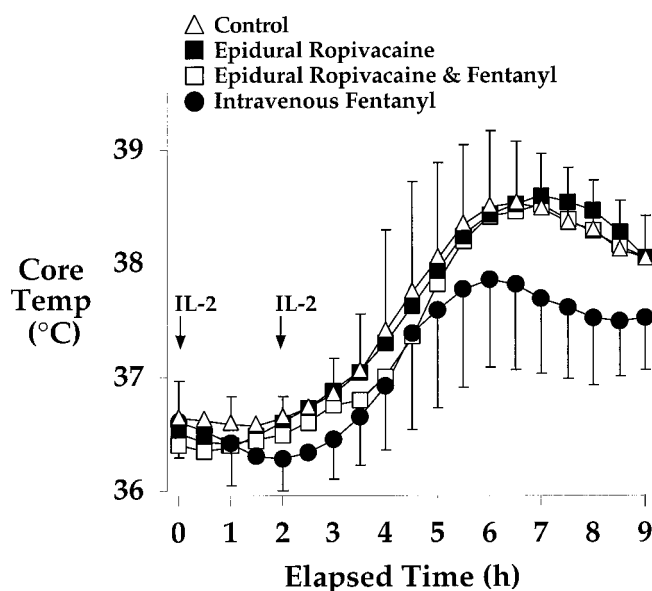P_{CO_2} = partial pressure of carbon dioxide.

Fig. 1. Core temperatures after administration of 50 IU/g of interleukin (IL) 2 followed by a second dose of 100 IU/g, 2 h later. The first dose of IL-2 defined elapsed time 0. Data are presented as mean ± SD. Error bars for the epidural days are omitted for clarity, but were similar to those shown for control and intravenous fentanyl. See table 2 for statistical analysis.

Core temperatures peaked at 38.7 ± 0.6°C on the control day, at 38.7 ± 0.7°C during epidural ropivacaine, at 38.7 ± 0.9°C with combined epidural ropivacaine-fentanyl, but only at 38.1 ± 0.7°C during intravenous fentanyl (table 2). Fentanyl significantly reduced the febrile response to pyrogen, decreasing integrated core temperature from 7.0 ± 3.2°C · h on the control day to 3.8 ± 3.0°C · h on the intravenous fentanyl day. In contrast, epidural ropivacaine and epidural ropivacaine-fentanyl did not inhibit manifestation of fever (fig. 1).

The fraction of core-temperature measurements that exceeded 38°C was halved by intravenous fentanyl. The fraction of measurements exceeding 38.5°C was reduced more than fivefold by intravenous fentanyl (table 3). Both these reductions were statistically significant ($P < 0.001$).

Plasma concentration of TNF α, IL-6, and IL-8 increased later, reaching peak concentrations after 4 or 5 elapsed h. All subsequently decreased to near-baseline values by 8 or 9 elapsed h. In contrast, IL-10 continued to increase throughout the study period. None of the cytokine concentrations differed significantly on the four study days.

Discussion

Epidural analgesia is associated with a high incidence of hyperthermia,[1,5,8] which provokes expensive and invasive interventions.[6,7] Because passive hyperthermia and excessive heat production are unlikely causes, elevated body temperature in laboring and postoperative patients is presumably true fever resulting from infection, tissue damage atelectasis, and so forth. The conventional understanding is that hyperthermia associated with epidural analgesia in the same clinical situation is caused by epidural analgesia. However, this theory is inconsistent with our observation that epidural analgesia failed to influence febrile responses. Instead, our data suggest that fever is inhibited by opioid administration in the "control" subjects.

Although maximum and average core temperatures differed by less than 1°C when the volunteers were given fentanyl and epidural analgesia, integrated temperature was halved by low-dose fentanyl. More importantly, the fraction of core temperatures exceeding various temperatures was reduced by a factor of two to five. This is a critical outcome because temperatures exceeding specific values often trigger laboratory investigations for infection and even antibiotic administration. That intravenous fentanyl reduces the fraction of temperatures exceeding various threshold temperatures thus explains the high incidence of "fever work-ups" in laboring mothers and their children after epidural analgesia.[6,7] It is also consistent with the fact that there is no evidence whatsoever suggesting that these additional infection investigations were otherwise justified or in any way influenced outcome.[2]

Published reports demonstrate a correlation between hyperthermia during epidural analgesia and clinical signs of infection.[24] There is also evidence that hyperthermia during epidural analgesia is highly associated with placental inflammation.[25] These authors concluded: "Epidural analgesia is associated with intrapartum fever, but only in the presence of placental inflammation. This suggests that the fever reported with epidural analgesia results from immune responses rather than the analgesia itself." These results are consistent with our theory that hyperthermia during epidural analgesia is associated with inflammation (although not necessarily infection). Our results thus suggest that hyperthermia during epidural analgesia should be taken seriously and not con-

Table 3. Core Temperatures Exceeding 38.0, 38.5, and 39.0°C

	Control	Epidural Ropivacaine	Epidural Ropivacaine and Fentanyl	Intravenous Fentanyl	P
> 38.0°C	72	68	69	28	< 0.001
> 38.5°C	31	46	39	6	< 0.001
> 39.0°C	16	17	20	2	0.059

The percentage of measurements, during the 3–8 elapsed hour period, in which core temperatures exceeded 38.0, 38.5, or 39.0°C.

sidered a benign complication of the anesthetic technique *per se*. In contrast, threshold temperatures triggering investigations for infection should probably be reduced by approximately 0.5°C in patients given opioid analgesia.

Opioids are frequently administered epidurally because they augment analgesia with little respiratory compromise.[26] Relatively little opioid is required in the epidural space compared with intravenous administration, and the dose we used was typical.[26,27] Plasma fentanyl concentrations were six- to sevenfold lower after epidural than intravenous administration of the drug, which is consistent with the relatively small epidural dose.[28] Furthermore, pupil size and reflex amplitude (which are excellent measures of opioid effect) were essentially unchanged by epidural fentanyl. As may be expected from these data, epidural fentanyl had no detectable influence on the febrile response.

We have previously demonstrated that opioid-induced inhibition of fever is mediated centrally, rather than by a reduction in peripheral concentrations of pyrogens, when opioids are given after IL-2.[9] Our current results confirm this observation and extend it to the case in which opioids are given before induction of fever. Epidural analgesia did not inhibit fever and, not surprisingly, also failed to reduce circulating pyrogen concentrations.

We evaluated volunteers rather than patients. Responses under clinical circumstances are likely to differ somewhat. Nonetheless, it remains likely that the cause we propose for hyperthermia associated with epidural analgesia applies widely. Our theory does not exclude other causes of hyperthermia during epidural analgesia; it therefore remains likely that other yet-to-be-identified mechanisms also contribute.

In summary, the conventional assumption is that hyperthermia during epidural analgesia is caused by the technique. We tested an alternative theory that fever in humans is manifested normally during epidural analgesia, but suppressed by low-dose opioid. Intravenous fentanyl halved the febrile response to pyrogen, whereas epidural ropivacaine and epidural ropivacaine–fentanyl did not inhibit fever. These data support our proposed mechanism for hyperthermia during epidural analgesia and suggest that hyperthermia during epidural analgesia should thus be taken seriously and not considered a benign complication of the anesthetic technique *per se*.

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