

Meperidine Decreases the Shivering Threshold Twice as Much as the Vasoconstriction Threshold

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Background: Meperidine administration is a more effective treatment for shivering than equianalgesic doses of other opioids. However, it remains unknown whether meperidine also profoundly impairs other thermoregulatory responses, such as sweating or vasoconstriction. Proportional inhibition of vasoconstriction and shivering suggests that the drug acts much like alfentanil and anesthetics but possesses greater thermoregulatory than analgesic potency. In contrast, disproportion-

ate inhibition would imply a special antishivering mechanism. Accordingly, the authors tested the hypothesis that meperidine administration produces a far greater concentration-dependent reduction in the shivering than vasoconstriction threshold.

Methods: Nine volunteers were each studied on three days: 1) control (no opioid); 2) a target total plasma meperidine concentration of 0.6 $\mu\text{g/ml}$ (40 mg/h); and 3) a target concentration of 1.8 $\mu\text{g/ml}$ (120 mg/h). Each day, skin and core temperatures were increased to provoke sweating and then subsequently reduced to elicit vasoconstriction and shivering. Core temperature thresholds (at a designated skin temperature of 34°C) were computed using established linear cutaneous contributions to control sweating (10%) and vasoconstriction and shivering (20%). The dose-dependent effects of unbound meperidine on thermoregulatory response thresholds was then determined using linear regression. Results are presented as means \pm SDs.

Results: The unbound meperidine fraction was $\approx 35\%$. Meperidine administration slightly increased the sweating threshold ($0.5 \pm 0.8^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$; $r^2 = 0.51 \pm 0.37$) and markedly decreased the vasoconstriction threshold ($-3.3 \pm 1.5^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$; $r^2 = 0.92 \pm 0.08$). However, meperidine reduced the shivering threshold nearly twice as much as the vasoconstriction threshold ($-6.1 \pm 3.0^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$; $r^2 = 0.97 \pm 0.05$; $P = 0.001$).

Conclusions: The special antishivering efficacy of meperidine results at least in part from an uncharacteristically large reduction in the shivering threshold rather than from exaggerated generalized thermoregulatory inhibition. This pattern of thermoregulatory impairment differs from that produced by alfentanil, clonidine, propofol, and the volatile anesthetics, all which reduce the vasoconstriction and shivering thresholds comparably. (Key words: Anesthesia. Opioids: alfentanil; meperidine; pethidine. Temperature. Thermoregulation: shivering; sweating; vasoconstriction.)

GENERAL anesthetics markedly impair thermoregulatory control, producing a characteristic slight increase in the sweating threshold (triggering core temperature) combined with a marked and comparable reduction in the vasoconstriction and shivering thresholds.¹⁻³ Alfentanil, a nearly pure μ -receptor agonist, produces a similar pattern of thermoregulatory inhibition, although the magnitude is somewhat less.⁴

Meperidine possesses special antishivering proper-

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ties. That is, meperidine prevents or manages shivering far better than roughly equianalgesic doses of other opioids.⁵⁻⁷ Meperidine possesses numerous nonopioid effects, including electroencephalographic (EEG) activation,⁸ lethal hyperthermia when combined with monoamine oxidase inhibitors,⁹ positive inotropy,¹⁰ local anesthetic properties,¹¹ and a central anticholinergic action.⁸ Nonetheless, the special antishivering effect of meperidine appears related to its $\approx 10\%$ activity at kappa opioid receptors.¹² This theory is supported by observations that moderate-dose naloxone only partially blocks the antishivering effect of meperidine and that butorphanol (also a partial κ -receptor agonist) stops shivering better than fentanyl.¹³

Despite clinical observations that meperidine possesses special antishivering efficacy,⁵⁻⁷ the drug's thermoregulatory physiology remains unexplored. For example, it is unknown whether meperidine also profoundly impairs other thermoregulatory responses such as sweating or vasoconstriction. The issue is important because the drug's efficacy could be mediated by general thermoregulatory impairment or by a special action on shivering.

Proportional inhibition of thermoregulatory control suggests that the drug acts much like an anesthetic,¹⁴⁻¹⁶ but possesses greater thermoregulatory than analgesic potency. In contrast, disproportionate inhibition of shivering would imply a special antishivering mechanism. Accordingly, we tested the hypothesis that meperidine administration produces a far greater concentration-dependent reduction in the shivering than vasoconstriction threshold.

Methods

With approval from the Committee on Human Research at the University of California in San Francisco and informed consent, we studied nine healthy male volunteers. Morphometric characteristics included age, 31 ± 6 yr; weight, 72 ± 6 kg; height, 177 ± 4 cm; and body fat, $20 \pm 2\%$.¹⁷ The volunteers fasted 8 hours before arriving at the laboratory, which was maintained near 22 or 23°C . They were minimally clothed during the protocol and rested supine on a standard operating room table. The studies were conducted from July through October 1994. Five of the volunteers participated in a similar, near-simultaneous evaluation of alfentanil.⁴

Treatment Protocol

The volunteers were each evaluated on three separate study days. To avoid circadian fluctuations, studies were scheduled so that thermoregulatory responses were triggered at similar times on each of the days. An intravenous catheter was inserted in the left forearm for fluid and meperidine administration. Fluid was administered as necessary to maintain mean arterial blood pressure > 60 mmHg. A 14-g catheter was inserted in a right antecubital vein and used for blood sampling.

Meperidine was administered intravenously using a computer-controlled syringe pump (Ohmeda 9000, Ohmeda Inc., Steeton, England). The infusion profile was based on plasma efflux,¹⁸ with coefficients estimated from published pharmacokinetic data.^{19,20} The pump was adjusted to provide a target total meperidine plasma concentration of $0.6 \mu\text{g/ml}$ (≈ 40 mg/h) on the first study day. The second study day served as a control (no drug infusion), and a meperidine plasma concentration of $1.8 \mu\text{g/ml}$ (≈ 120 mg/h) was targeted on the final study day. To minimize the effects of tolerance,²¹ the lower meperidine dose was always studied first, and at least 2 weeks were allowed between the two meperidine days.

Thermal manipulation started after 15 min of meperidine administration. Before warming, the volunteers were wrapped in plastic to minimize evaporative heat loss. Throughout the protocol, arms were protected from active warming and cooling to avoid locally mediated vasomotion.²² All other skin below the neck was similarly manipulated throughout each study day.

Skin and core temperatures were first gradually increased with a forced-air warmer and circulating-water mattress until sweating was observed. Skin and core temperatures then were gradually decreased using the circulating-water mattress and a forced-air cooler.²³ As in previous studies,^{2,3} the sweating threshold was determined first because this threshold deviates least from normal body temperature. This protocol allowed a considerably shorter study day than if we had first cooled to the shivering and then rewarmed all the way to sweating threshold. The study ended each day when shivering was detected. Skin and core temperature changes were restricted to less than 2°C/h because this rate is unlikely to trigger dynamic thermoregulatory responses.²⁴

Measurements

Heart rate and oxyhemoglobin saturation (S_{pO_2}) were measured continuously using pulse oximetry, and blood

pressure was determined oscillometrically at 5-min intervals at the left ankle. Expiratory carbon dioxide concentrations were measured from a catheter inserted into one nostril using a Rascal® monitor (Ohmeda Inc., Salt Lake City, UT); exhaust gas from this monitor was returned to a DeltaTrac™ oxygen consumption monitor (SensorMedics Corp., Yorba Linda, CA).

Core temperature was recorded from the tympanic membrane using Mon-a-Therm® thermocouples (Malinckrodt Anesthesiology Products, Inc., St. Louis, MO). The aural probes were inserted by the volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected a gentle rubbing of the attached wire. The aural canal was occluded with cotton, the probe securely taped in place, and a gauze bandage positioned over the external ear. Mean skin-surface temperature was calculated from measurements at 15 area-weighted sites.^{25,26} Temperatures were recorded at 5-min intervals from thermocouples connected to calibrated Iso-Thermex® thermometers having an accuracy of 0.1° C and a precision of 0.01° C (Columbus Instruments, Corp., Columbus, OH).

Sweating was continuously quantified on the left upper chest, just below the clavicle, using a ventilated capsule.^{27,28} As in previous studies,⁴ sustained sweating more than 40 g · m⁻² · h⁻¹ defined the sweating threshold. Absolute right middle fingertip blood flow was quantified using venous-occlusion volume plethysmography at 5-min intervals;²⁹ as in our previous evaluation of opioids,⁴ a sustained decrease in fingertip blood flow to less than 0.25 ml/min identified intense vasoconstriction.

Shivering was evaluated using oxygen consumption as measured by the DeltaTrac™ metabolic monitor. The system was used in canopy-mode, and measurements were averaged for 1-min intervals and recorded every 5 min. (In this mode, 40 l/min is aspirated by the metabolic monitor from a plastic bubble surrounding the head and upper chest.) A sustained increase in oxygen consumption to 130% of baseline values identified significant shivering.

Venous blood was sampled at the time of sweating, vasoconstriction, and shivering for measurement of meperidine blood concentrations. To determine the concentration of unbound meperidine and normeperidine, 1 ml of fresh plasma from each blood sample was centrifuged using the Micro-partition System MPS-1 with YMT membrane (Amicon, Inc., Beverly, MA) for 30 min. The ultrafiltrate and the plasma samples were stored at

-20° C until meperidine concentrations were determined using high-performance liquid chromatography.

To evaluate meperidine concentrations, plasma (800 µl) or ultrafiltrate (150–250 µl) were alkalized with 100 µl 3 M NaOH and extracted into 6 ml pentane, along with 25 µl/ml of ropivacaine as an internal standard, and back extracted into 125 µl 1.5 mM orthophosphoric acid. The mobile phase was 100:10:1 acetonitrile: methanol 20 mM K₂HPO₄ at pH 7.0, running through a 150 mm × 3.9 mm µBondapac CN column (Waters Associates, Milford, MA) at a rate of 1.5 ml/min with detection by ultraviolet absorbance at 205 nm. This assay is linear to at least 10 µg/ml, with a detection limit of 0.005 µg/ml with an 80-µl injection and within-day coefficient of variation of 4.1% (n = 6) at 0.25 µg/ml.

Pupil diameter and light-reflex amplitude correlate well with opioid effect.³⁰ Consequently, pupillary responses were used to evaluate pharmacodynamic effects of meperidine. A portable infrared pupillometer (Fairville Medical Optics, Inc., Amersham, Buckinghamshire, England) was used to measure the pupillary response. The pupillometer was programmed to provide a 0.5-s, 130 candela/m² pulse of green light and to scan the pupil at a rate of 10 Hz for 2 s from the beginning of the light stimulus. Pupillary diameter and light reflex amplitude from the right eye were measured three times in succession at each threshold, and the resulting values averaged. Ambient light was maintained near 150 lux, and the left eye was kept covered during the measurements. We previously have described use of this pupillometer.³¹

Data Analysis

Hemodynamic responses and ambient temperature and humidity on each study day were first averaged within each volunteer; the resulting values then were averaged among volunteers. Results are presented as mean ± SD. All the physiologic effects of meperidine are reported in terms of unbound (active) concentrations. Results for each study day were compared using repeated-measures analysis of variance and Scheffé's F test. Mean skin temperatures, end-tidal P_{CO2}, and pupillary responses at the sweating, vasoconstriction, and shivering thresholds were similarly compared. Meperidine blood concentrations and unbound meperidine fraction were compared at the thresholds using two-tailed, paired *t* tests.

Core-temperature response thresholds were determined by arithmetically compensating for alterations in skin temperature using a previously described model.³

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The coefficient of cutaneous contribution (β) was taken as 0.1 for sweating³² and 0.2 for vasoconstriction and shivering.³³ The designated skin temperature was set at 34° C because that is a typical intraoperative value.

From the calculated core-temperature thresholds on each of the three study days, unbound meperidine concentration-response curves for the sweating, vasoconstriction, and shivering thresholds were determined using linear regression. The average slopes and correlation coefficients (r^2) for the nine volunteers then were computed from these values. The effect of unbound meperidine on pupillary responses was similarly computed using linear regression. Additionally, a single regression for each thermoregulatory response was determined from the combined data from all nine volunteers.

The concentration-dependence of pupillary and thermoregulatory responses in our current volunteers was compared with those previously given alfentanil using linear regression.³⁴ The ratio of the slopes, therefore, evaluated the relative potency of each opioid for each response.

Results

Volunteers typically were mildly sedated when the target total plasma meperidine concentration was 0.6 $\mu\text{g/ml}$ and deeply sedated when the target concentration was 1.8 $\mu\text{g/ml}$. Total plasma meperidine concentrations were essentially constant during the study. In contrast, normeperidine concentrations increased throughout the infusion. None of the volunteers required mechanical ventilatory assistance. However, most required verbal reminders to breathe at the lower target meperidine concentration, and all required frequent reminders at the higher target concentration. Ambient temperatures and blood pressures were comparable on each of the study days. Expired P_{CO_2} differed significantly at the highest meperidine concentration, but neither difference was clinically important. Heart rate also increased significantly at the highest dosage, by ≈ 10 beats/min (table 1).

Mean skin and core temperatures at sweating, vasoconstriction, and shivering, and the thresholds calculated from these values are shown in table 2. The sweating-to-vasoconstriction interthreshold range increased progressively as the meperidine concentration was increased. Unbound plasma meperidine decreased the core temperature triggering vasoconstriction by $3.3 \pm 1.5^\circ \text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$ ($r^2 = 0.92 \pm 0.08$) and shivering by 6.1

$\pm 3.0^\circ \text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$ ($r^2 = 0.97 \pm 0.05$). Shivering was thus inhibited nearly twice as much as vasoconstriction ($P = 0.001$). In contrast, increasing meperidine blood concentration increased the sweating threshold only slightly (slope = $0.5 \pm 0.8^\circ \text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$; $r^2 = 0.51 \pm 0.37$; fig. 1). Figure 2 shows the regressions for each threshold in terms of unbound plasma meperidine concentration, this time calculated using the combined data from all volunteers.

Pupil size and reflex amplitude decreased progressively as a function of meperidine concentration; however, the concentrations were similar at the sweating, vasoconstriction, and shivering thresholds on each study day (table 2). Absolute reflex amplitude also was markedly reduced from 2.2 to 1.3 to 0.5 mm as the meperidine concentration increased. In contrast, reflex amplitude, expressed as a percentage of pupil size, was similar on the control and 0.6 $\mu\text{g/ml}$ day and decreased only $\approx 35\%$ at the highest meperidine concentration. Pupillary responses at each target concentration were virtually identical in our current volunteers and in those given alfentanil in a previous, similar study.⁴

The ratio of the concentration-dependence slopes for vasoconstriction, pupil size, and absolute reflex amplitude were ≈ 20 . In contrast, the ratio for shivering was 10, indicating that meperidine inhibits shivering far more than vasoconstriction and more than roughly equivalent concentrations of alfentanil (table 3).

Discussion

Meperidine slightly increased the sweating threshold while markedly reducing the threshold for vasoconstriction. The sweating-to-vasoconstriction interthreshold range¹ increased sevenfold from its control values of 0.3°C to $\approx 2.1^\circ \text{C}$ at the highest meperidine concentration. This pattern of thermoregulatory impairment is similar to that produced by propofol³ and volatile anesthetics.² Further, the extent to which sweating and vasoconstriction were inhibited was similar in our current volunteers given meperidine and in those who were previously given roughly equianalgesic plasma concentrations of alfentanil.⁴ Meperidine, like alfentanil and anesthetics, thus markedly impairs thermoregulatory control.

Clonidine,³⁵ alfentanil,⁴ propofol,³ and the volatile anesthetics^{1,2} comparably decrease the vasoconstriction and shivering thresholds. In marked contrast, meperidine decreased the shivering threshold twice as much as the vasoconstriction threshold. The special antishiv-

Table 1. Environmental and Anesthetic Data, Total Plasma Meperidine and Normeperidine Concentrations, and Unbound Fractions

Target [Meperidine]	Control	Low-dose	High-dose
Ambient temperature (°C)	22.3 ± 0.3	22.4 ± 0.8	23.0 ± 0.8
Relative humidity (%)	42 ± 2	42 ± 1	40 ± 2*,†
Mean arterial blood pressure (mmHg)	92 ± 8	91 ± 7	90 ± 19
Heart rate (bpm)	59 ± 7	58 ± 6	70 ± 11*,†
Expired P _{CO₂}	38 ± 2	41 ± 2*	45 ± 4*,†
[Total meperidine] at sweating (μg/ml)	—	0.4 ± 0.1	1.3 ± 0.3†
[Total meperidine] at vasoconstriction (μg/ml)	—	0.4 ± 0.1	1.2 ± 0.2†
[Total meperidine] at shivering (μg/ml)	—	0.4 ± 0.1	1.3 ± 0.3†
Unbound meperidine (%)	—	34 ± 7	33 ± 7
[Total normeperidine] at sweating (μg/ml)	—	0.04 ± 0.01	0.10 ± 0.04†
[Total normeperidine] at vasoconstriction (μg/ml)	—	0.05 ± 0.01	0.14 ± 0.04†
[Total normeperidine] at shivering (μg/ml)	—	0.07 ± 0.02	0.19 ± 0.05†
Unbound normeperidine (%)	—	31 ± 10	31 ± 10

Values are mean ± SD.

* Statistically significant difference from control.

† Significant difference between a target concentration of 0.6 and 1.8 μg/ml.

ering action of meperidine does not, therefore, result simply from a generalized thermoregulatory effect exceeding that expected from the drug's analgesic po-

tency. Instead, shivering appears specifically targeted. It is likely that other κ -receptor opioids manifest similar special antishivering activity.

Table 2. Mean Skin and Core Temperatures, Calculated Thresholds (Assuming a 34°C Skin Temperature), and Pupillary Responses

Target [Meperidine]	Control	Low-dose	High-dose
Sweating			
Mean skin (°C)	36.2 ± 0.4	36.4 ± 0.4	36.7 ± 0.3
Core (°C)	36.9 ± 0.2	36.9 ± 0.2	37.1 ± 0.2
Threshold (°C)	37.1 ± 0.3	37.2 ± 0.2	37.4 ± 0.3*,†
Pupil diameter (mm)	6.0 ± 0.6	3.8 ± 1.0*	2.2 ± 1.0*,†
Reflex amplitude (mm)	2.2 ± 0.4	1.4 ± 0.4*	0.6 ± 0.4*,†
Reflex amplitude (%)	36 ± 7	37 ± 7	27 ± 7*,†
Vasoconstriction			
Mean skin (°C)	33.4 ± 0.6	32.2 ± 0.7	31.1 ± 1.3
Core (°C)	36.9 ± 0.2	36.5 ± 0.3	36.1 ± 0.5
Threshold (°C)	36.8 ± 0.3	36.1 ± 0.4*	35.3 ± 0.7*,†
Pupil diameter (mm)	5.9 ± 0.6	3.5 ± 0.8*	2.2 ± 1.0*,†
Reflex amplitude (mm)	2.2 ± 0.4	1.3 ± 0.3*	0.6 ± 0.4*,†
Reflex amplitude (%)	40 ± 8	37 ± 7	25 ± 7*,†
Shivering			
Mean skin (°C)	29.8 ± 1.3	27.9 ± 1.5	26.5 ± 1.9
Core (°C)	36.8 ± 0.2	36.2 ± 0.4	35.4 ± 0.9
Threshold (°C)	35.7 ± 0.5	34.7 ± 0.6*	33.5 ± 1.3*,†
Pupil diameter (mm)	6.0 ± 0.5	3.4 ± 1.1*	2.0 ± 0.5*,†
Reflex amplitude (mm)	2.1 ± 0.3	1.2 ± 0.5*	0.4 ± 0.2*,†
Reflex amplitude (%)	36 ± 6	36 ± 8	20 ± 7*,†

Values are mean ± SD. Statistical analysis was applied to all pupillary measurements, but only to the threshold temperatures.

* Statistically significant difference from control.

† Significant difference between a target concentration of 0.6 and 1.8 μg/ml.

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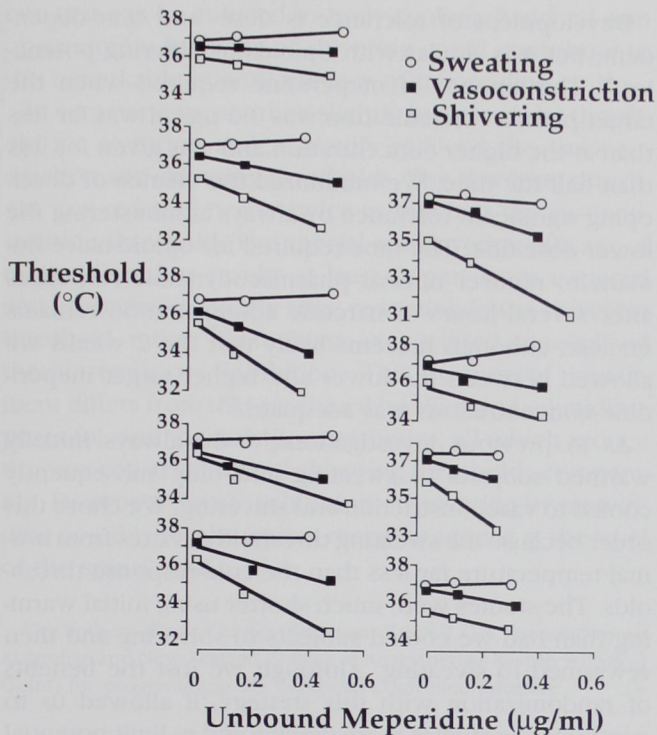


Fig. 1. The effect of increasing unbound plasma meperidine concentration on the core temperatures triggering sweating (open circles), vasoconstriction (filled squares), and shivering (open squares) in nine volunteers. Meperidine reduced the shivering threshold nearly twice as much as the vasoconstriction threshold, 6.1 ± 3.0 and $3.3 \pm 1.5^\circ \text{C } \mu\text{g/ml}$, respectively ($P = 0.001$). The sweating threshold, however, increased only slightly ($0.5 \pm 0.8^\circ \text{C } \mu\text{g/ml}$). The thresholds (at a designated skin temperature of 34°C) were calculated from measured skin and core temperatures.

Because only systemic responses were evaluated, we cannot determine the site at which meperidine acts on shivering. However, kappa receptors are mostly located in the spinal cord. Further, shivering—more than other thermoregulatory responses—appears to be controlled at the level of the spinal cord.^{36–38} The special antishivering activity of meperidine may thus be mediated by the spinal cord. This site contrasts with thermoregulatory inhibition routinely produced by μ -receptor agonists, which is presumably largely hypothalamic. Meperidine, having μ and kappa activity, will act at each site. We thus can postulate that meperidine reduces the vasoconstriction threshold via μ effect in the hypothalamus, whereas the shivering threshold is reduced by hypothalamic μ effect and by kappa activity at the level of the cord. To the extent that this paradigm is correct, it suggests that the drug's antishivering action is compa-

table at each site, thus producing twice the effect of a pure μ -receptor agonist.

Bound and unbound normeperidine concentrations increased throughout the infusion period. This is a natural consequence of the drug's relatively slow metabolism and occurs even when the meperidine concentration is kept constant by a computer-controlled infusion. Normeperidine concentrations were thus significantly greater at the shivering threshold than at the vasoconstriction and sweating thresholds—although the levels never exceeded 10% of the total plasma concentration of meperidine. High concentrations of normeperidine can cause seizures,^{39,40} but the drug probably has weak opioid properties. Further, pupillary responses were comparable at the beginning and end of each study, despite the progressive increase in the normeperidine concentration. It therefore seems unlikely that normeperidine has substantial thermoregulatory consequences. A limitation of our protocol is that we did not indepen-

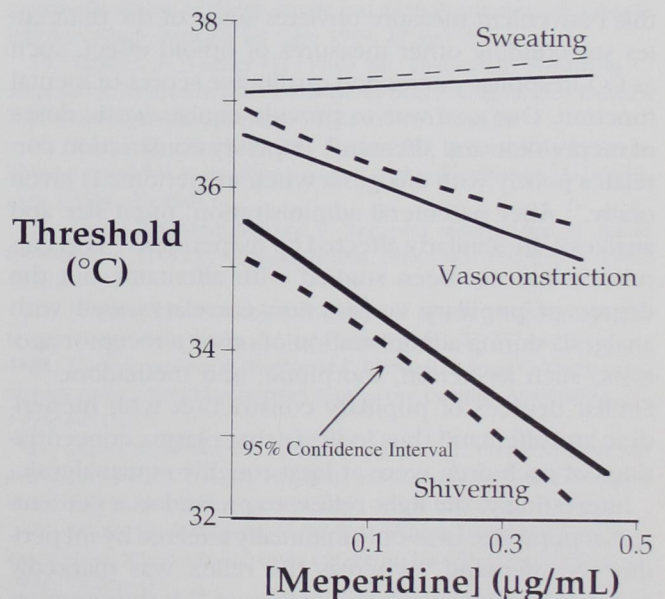


Fig. 2. The sweating threshold increased as a function of unbound plasma meperidine concentration: Sweating = $0.5[\text{meperidine } (^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml})] + 37.1$, $r^2 = 0.10$. In contrast, meperidine produced a linear decrease in the core temperature triggering vasoconstriction: Vasoconstriction = $-3.0[\text{meperidine } (^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml})] + 36.6$, $r^2 = 0.54$. Meperidine decreased the shivering threshold nearly twice as much as the vasoconstriction threshold: Shivering = $-5.6[\text{meperidine } (^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml})] + 35.6$, $r^2 = 0.62$. Dashed lines indicate 95% confidence intervals. These regression slopes differ from those reported in fig. 1 because they were calculated from the combined values in all volunteers rather than from individual data.

Table 3. Concentration Dependence of Thermoregulatory and Pupillary Responses during Meperidine and Alfentanil Administration

	Alfentanil Slope	Meperidine Slope	Ratio
Vasoconstriction ($^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$)	-75 ± 67	-3.3 ± 1.5	23
Shivering ($^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$)	-63 ± 37	-6.1 ± 3.0	10
Pupil size ($\text{mm} \cdot \mu\text{g}^{-1} \cdot \text{ml}$)	-185 ± 60	-8.7 ± 4.2	21
Absolute reflex amplitude ($\text{mm} \cdot \mu\text{g}^{-1} \cdot \text{ml}$)	-79 ± 19	-3.8 ± 1.9	20

Slopes during both alfentanil and meperidine administration were calculated using unbound drug concentrations. The sweating thresholds were precluded from this analysis because the slopes were too small to permit meaningful comparison. Similarly, percentage reflex amplitude was excluded because the data were not linear. The ratios of the vasoconstriction and pupillary slopes were comparable, near 20. In contrast, the shivering slope ratio was half as great, consistent with the special antishivering action of meperidine.

dently evaluate the thermoregulatory effects of meperidine and normeperidine.

We used pupil size as a measure of opioid effect. Pupil size is easily obtained with infrared pupillometry, and this convenient measure obviates some of the difficulties surrounding other measures of opioid effect, such as CO_2 -response curves and qualitative scores of mental function. Our goal was to provide equianalgesic doses of meperidine and alfentanil. Pupillary constriction correlates poorly with analgesia when meperidine is given orally.⁴¹ After parenteral administration, pupil size and analgesia are similarly affected by meperidine.² This correlation has not been studied with alfentanil, but the degree of pupillary constriction correlates well with analgesia during administration of other μ -receptor agonists, such as heroin, morphine, and methadone.^{30,42} Similar degrees of pupillary constriction with meperidine and alfentanil thus indicate that plasma concentrations of each drug were at least roughly equianalgesic.

Interestingly, the light reflex, expressed as a percentage of pupil size, was only minimally affected by meperidine or alfentanil,⁴ whereas the reflex was markedly reduced by isoflurane³¹ and enflurane.⁴³ It thus appears that the percentage reflex amplitude is relatively well maintained during opioid administration, despite markedly reduced pupil size. In contrast, volatile anesthetics reduce the reflex amplitude more than pupil size. Differing effects on pupil size and the reflex amplitude with these two classes of drugs could possibly be exploited to independently evaluate "depth-of-anesthesia" (volatile anesthetic effect) and analgesia (opioid effect).

Development of tolerance is dose- and time-dependent, but it is similar with opioids of differing potencies.⁴⁴ The amount of meperidine required when the target plasma concentration was $0.6 \mu\text{g}/\text{ml}$ was far less than at the higher concentration and was given for less than half the time. We minimized the chance of developing significant tolerance by always administering the lower dose first. The time required for opioid-naïve humans to recover normal pharmacodynamic responses after several hours of narcotic administration remains unclear, although it seems likely that the 2 weeks we allowed between the lower and higher target meperidine concentrations was adequate.²¹

As in previous investigations,^{3,4} we always initially warmed subjects to sweating and only subsequently cooled to vasoconstriction and shivering. We chose this order because the sweating threshold deviates from normal temperature far less than the cold-response thresholds. The studies were much shorter using initial warming than had we cooled subjects to shivering and then rewarmed to sweating. Although we lost the benefits of randomization with this strategy, it allowed us to complete the studies more quickly and to limit potential for opioid tolerance.

The validity of our comparison between the thermoregulatory effects of alfentanil and meperidine is potentially limited because the studies were not exactly contemporaneous and because only half the volunteers participated in both. However, it is unlikely that relevant characteristics of the volunteers changed significantly: all were young, healthy men who avoided opioids and recreational drugs.

Another factor limiting comparison between our current and previous studies is that the equianalgesic plasma concentrations of meperidine and alfentanil remain unclear. Previous work on clinical analgesic efficacy suggests an $\approx 6:1$ total concentration ratio between meperidine and alfentanil.^{45,46} The actual total meperidine-to-alfentanil ratio in our two studies was only $\approx 4:1$. However, pupillary responses—a reliable measure of opioid effect³⁰—were virtually identical in the two studies. Additionally sedation levels, evaluated informally, also were similar. It seems likely that the meperidine and alfentanil doses in our two studies were roughly equianalgesic.

An additional limitation of this study is that we evaluated neither the gain nor the maximal intensity of shivering. Gain is defined by the rate at which shivering increases, once triggered, with additional core cooling. Maximum intensity is the largest increase in metabolic

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rate that can be induced by body cooling. Reduced gain or maximum intensity of shivering could contribute to the remarkable clinical efficacy of meperidine.

In summary, meperidine slightly increased the threshold for sweating and markedly reduced the vasoconstriction and shivering thresholds. The shivering threshold was reduced nearly twice as much as the vasoconstriction threshold. The special antishivering efficacy of meperidine thus results at least in part from a special and uncharacteristically large reduction in the shivering threshold rather than from exaggerated generalized thermoregulatory inhibition. This pattern of impairment differs from that produced by alfentanil, clonidine, propofol, and the volatile anesthetics, all which reduce the vasoconstriction and shivering thresholds comparably. Disproportionate inhibition of shivering by meperidine possibly results from κ -receptor agonist at the level of the spinal cord.

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