Meperidine and Alfentanil Do Not Reduce the Gain or Maximum Intensity of Shivering

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Background: Thermoregulatory shivering can be characterized by its threshold (triggering core temperature), gain (incremental intensity increase with further core temperature deviation), and maximum intensity. Meperidine (a combined μ- and κ-agonist) treats shivering better than equianalgesic doses of pure μ-opioid agonists. Meperidine's special antishivering action is mediated, at least in part, by a disproportionate decrease in the shivering threshold. That is, meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold, whereas alfentanil (a pure μ-agonist) decreases the vasoconstriction and shivering thresholds comparably. However, reductions in the gain or maximum shivering intensity might also contribute to the clinical efficacy of meperidine. Accordingly, we tested the hypothesis that meperidine reduces the gain and maximum intensity of shivering much more than alfentanil does.

Methods: Ten volunteers were each studied on three separate days: (1) control (no drug); (2) a target total plasma meperidine concentration of 1.2 μg/ml; and (3) a target plasma alfentanil concentration of 0.2 μg/ml. Skin temperatures were maintained near 31°C, and core temperatures were decreased by central-venous infusion of cold lactated Ringer's solution until maximum shivering intensity was observed. Shivering was evaluated using oxygen consumption and electromyography. A sustained increase in oxygen consumption identified the shivering threshold. The gain of shivering was calculated as the slope of the oxygen consumption *versus* core temperature regression, and as the slope of electromyographic intensity *versus* core temperature regression.

Results: Meperidine and alfentanil administration significantly decreased the shivering thresholds. However, neither meperidine nor alfentanil reduced the gain of shivering, as determined by either oxygen consumption or electromyography. Opioid administration also failed to significantly decrease the maximum intensity of shivering.

Conclusions: The authors could not confirm the hypothesis that meperidine reduces the gain or maximum intensity of shivering more than alfentanil does. These results suggest that meperidine's special antishivering effect is primarily mediated by a disproportionate reduction in the shivering threshold. (Key words: Anesthesia; hypothermia; normeperidine; pethidine; thermoregulation; temperature.)

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MAJOR autonomic cold defenses include arteriovenous shunt vasoconstriction and shivering. These defenses can be characterized by their thresholds (triggering core temperature), gains (incremental intensity increase with further core temperature deviation), and maximum intensities.[1] Volatile[2,3] and intravenous anesthetics[4] and μ-opioid agonists[5] all produce concentration-dependent decreases in the shivering threshold. Meperidine (pethidine), however, has proved a far more effective treatment for shivering than equianalgesic doses of μ-opioid agonists.[6,7] This special antishivering activity
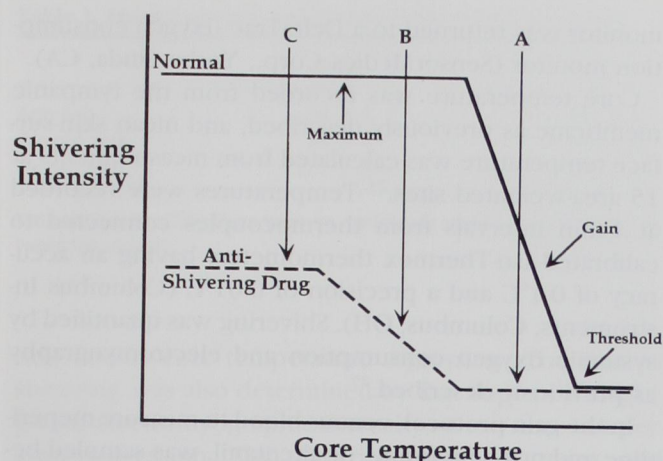
Fig. 1. A cartoon showing the three major components of shivering: threshold (triggering core temperature), gain (incremental intensity increase with further core temperature deviation), and maximum intensity. The normal case is illustrated with a solid line. Antishivering drugs, such as meperidine or clonidine, may reduce muscular activity by decreasing any or all aspects of the shivering response. In this illustration, we consider the case of a drug that decreases the threshold, gain, and maximum shivering intensity (*dashed line*). The effect of drug administration on shivering intensity depends on the volunteer's core temperature. Shivering will be obliterated when the drug reduces the threshold to less than body temperature (*A*). Shivering intensity, however, will be substantially reduced when body temperature remains less than the new shivering threshold but low gain restricts the amount of muscular activity (*B*). Finally, shivering will also be reduced even at very low body temperatures because maximum intensity is restricted (*C*). In a routine clinical trial, it would be difficult to determine which mechanism(s) contributed to a drug's antishivering action.

may result from meperidine's κ-receptor activation,[8] although the drug possesses a host of nonopioid activities that may also contribute.[9-13]

At a given level of residual anesthesia and body temperature, meperidine (or any other treatment) potentially decreases muscular activity by reducing the threshold, gain, or maximum shivering intensity. What happens when all three are reduced? In this case, three different mechanisms can contribute to a clinically observed reduction in shivering intensity. Shivering will be obliterated when meperidine reduces the threshold to less than body temperature. Shivering intensity, however, will be substantially reduced (although not eliminated) if body temperature remains less than the new shivering threshold, but low gain restricts the amount of muscular activity. Finally, shivering will also be reduced even at very low body temperatures if the maximum intensity is restricted. These three possibilities are shown in figure 1. In a typical clinical study, it would be

nearly impossible to distinguish among these potential mechanisms because each would eliminate or substantially reduce shivering in many patients.

Research has already established that meperidine's special antishivering action is manifested in part by a disproportionate decrease in the shivering threshold.[14] Specifically, meperidine decreases the shivering threshold twice as much as equianalgesic concentrations of alfentanil do.[5,14] Even this reduction, however, seems unlikely to be the sole explanation for the markedly greater clinical efficacy of meperidine in treating postoperative shivering. Thus meperidine may also inhibit shivering by reducing the gain or maximum intensity of shivering.

The effects of opioids on the gain and maximum intensity of shivering remain unknown and would be difficult to predict from previous studies because anesthetics reduce the gain of some thermoregulatory responses[15] but leave the gain and maximum intensity of others unchanged.[16,17] Accordingly, we tested the hypothesis that meperidine decreases the gain and maximum intensity of shivering more than equianalgesic concentrations of the pure μ-receptor agonist alfentanil do.

Normeperidine, the major metabolite of meperidine, has a longer half-life than the parent drug. Normeperidine thus inevitably accumulates even when a computer-controlled infusion maintains constant plasma meperidine concentrations. Sufficient concentrations of normeperidine can cause seizures and may be associated with muscular rigidity.[18,19] Accordingly, we confirmed that normeperidine accumulation during a prolonged meperidine infusion does not provoke rigidity or other muscular activity that might increase oxygen consumption, thereby confounding measurements of shivering gain and maximum intensity.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and informed consent, we studied 16 healthy men. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. To avoid circadian fluctuations, studies were scheduled so that thermoregulatory responses were triggered at similar times on each of the 3 days. The volunteers fasted for 8 h before each study day and rested supine on a standard operating room table. Ambient temperature was maintained near 22°C.

Gain Protocol

Ten minimally clothed volunteers participated in these studies. An intravenous catheter was inserted in the left forearm for meperidine and alfentanil administration. A 16-gauge catheter was inserted into the superior vena cava *via* the right internal jugular vein for cold fluid infusion and blood sampling.

Meperidine and alfentanil were administered using a computer-controlled syringe pump (Ohmeda model 9000, Steeton, UK). The infusion profile was based on a modification of the method of Kruger-Thiemer[20] and published data.[21] The pump was adjusted to provide target total meperidine or alfentanil plasma concentrations of 1.2 $\mu g/ml$ or 0.2 $\mu g/ml$, respectively. Meperidine or alfentanil, randomly assigned, was given on the first or third study days. The second study day served as a control (no drug infusion). To minimize the effects of opioid tolerance,[22] at least 2 weeks were allowed between the first and third study days.

Throughout the 3 study days, mean skin temperature was kept constant near 31°C using a forced-air cover (Augustine Medical, Eden Prairie, MN) and circulating-water mattress (Cincinnati Sub-Zero Products, Cincinnati, OH). Core cooling started 45 min after meperidine or alfentanil administration on the drug days or after 15 min of baseline measurements on the control day. The core was cooled by central-venous administration of lactated Ringer's solution at ≈3°C. The cooling rate was restricted to ≤2°C/h, because such rates are unlikely to trigger dynamic thermoregulatory responses.[23] Cooling ceased when shivering intensity no longer increased, despite a continued decrease in core temperature.

Normeperidine Protocol

Six men participated in these studies. An intravenous catheter was inserted in the left forearm for fluid and meperidine administration. A 14-gauge catheter was inserted in a right antecubital vein and used for blood sampling. After baseline measurements for 1 h, meperidine was administered using the system described before to a target meperidine blood concentrations of 1.2 $\mu g/ml$.

Measurements

Heart rate was 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 using an Ultima monitor (Datex, Helsinki, Finland) from a catheter inserted into one nostril; 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 as previously described, and mean skin-surface temperature was calculated from measurements at 15 area-weighted sites.[24] Temperatures were recorded at 1-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, Columbus, OH). Shivering was quantified by systemic oxygen consumption and electromyography as previously described.[25]

In the gain protocol, venous blood to measure meperidine and normeperidine, or alfentanil, was sampled before and 40 min after drug administration, at the beginning of shivering, and when maximum shivering was observed. In the normeperidine protocol, plasma concentrations of meperidine and normeperidine were measured every hour after starting meperidine administration. To determine the unbound opioid concentrations, 1 ml fresh plasma from each blood sample was centrifuged using the Micro-partition System MPS-1 with YM-T membrane (Amicon, Inc., Beverly, MA) for 30 min. The ultrafiltrate and the plasma samples were stored at −20°C until drug concentrations were determined using high-performance liquid chromatography, as previously described.[5,14]

Pupil diameter and light-reflex amplitude correlate well with the opioid effect.[26] Consequently, pupillary responses were used to evaluate pharmacodynamic effects of meperidine and alfentanil. A portable infrared pupillometer (Fairville Medical Optics, Amersham, Buckinghamshire, UK) was used to measure the pupillary response.[27] The pupillometer was programmed to provide a 0.5-s-long, 130 candela/m^2 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 twice in succession, before and 40 min after drug administration, and when maximum shivering was observed. Ambient light was maintained near 150 lux, and the left eye was kept covered during the measurements.

Data Analysis

Gain Protocol. A sustained increase in oxygen consumption identified the shivering threshold. Maximum intensity of shivering was identified by an oxygen consumption that failed to increase further despite continued reduction in core temperature. The gain of shivering was determined by the slope of oxygen consump-

Table 1. Morphometric and Demographic Characteristics

	Gain	Normeperidine
Age (yr)	28 ± 6	29 ± 5
Weight (kg)	78 ± 7	78 ± 12
Height (cm)	177 ± 8	184 ± 6

Data are mean ± SD. There were no statistically significant differences between the groups.

tion *versus* core temperature regression. The gain of shivering was also determined by the slope of the integrated electromyographic intensity *versus* core temperature regression. The shivering threshold, gains, and maximum intensity were determined by an investigator blinded to treatment and core temperature.

Hemodynamic responses, ambient temperature, relative humidity, and the end-tidal carbon dioxide pressure on each study day were first averaged within each volunteer; the resulting values were then averaged among volunteers. Results for the three study days were compared using repeated-measures analysis of variance and Scheffé's F test. The gains of shivering as determined by oxygen consumption and electromyography were nonparametrically distributed and thus compared using the Friedman test. Pupillary responses during meperidine and alfentanil administration were compared using two-tailed, paired *t* tests. Results are presented as means ± SDs; probability values <0.01 were considered significant.

Normeperidine Protocol. Oxygen consumption data for each 1 h were first averaged for each volunteer; the resulting values were then averaged among volunteers. Results were compared using repeated-measures analysis of variance and Dunnett's test. Results are presented as means ± SD; probability values <0.01 were considered significant.

Results

Morphometric and demographic characteristics of the volunteers in each protocol were similar (table 1).

Gain Protocol

Volunteers typically were mildly sedated when meperidine or alfentanil was administered. Total plasma meperidine and alfentanil concentrations were held essentially constant during the study. In contrast, normeperidine concentrations increased from 0.03 ± 0.02 μg/ml (at the

beginning of cold infusion) to 0.16 ± 0.05 μg/ml (at maximum shivering) during meperidine administration. Unbound fractions of meperidine and alfentanil were ≈41 and ≈8%, respectively. None of the volunteers required mechanical ventilatory assistance. However, most required verbal reminders to breathe during meperidine or alfentanil administration.

Pupil size and absolute reflex amplitude, and reflex amplitude expressed as a percentage of pupil size decreased significantly during meperidine and alfentanil administration; however, the values were similar during meperidine and alfentanil administration and remained virtually constant during shivering (table 2).

Ambient temperature, relative humidity, heart rate, blood pressure, and mean skin temperature were comparable on each of the study days. End-tidal carbon dioxide pressure was slightly but significantly higher during opioid administration than on the control day. Similarly, significantly more lactated Ringer's solution was required when meperidine or alfentanil were administered than on the control day.

Shivering thresholds during meperidine and alfentanil administration were significantly less than that on the control day. Meperidine decreased the shivering threshold 0.4°C more than alfentanil administration, although

Table 2. Total Plasma Meperidine and Alfentanil Concentrations, and Pupillary Responses

	Meperidine	Alfentanil
Concentration before shivering (μg/ml)	1.2 ± 0.2	0.20 ± 0.04
Concentration at the beginning of shivering (μg/ml)	1.1 ± 0.2	0.19 ± 0.03
Concentration at maximum shivering (μg/ml)	1.2 ± 0.2	0.20 ± 0.03
Preinfusion		
Pupil diameter (mm)	5.2 ± 0.8	5.2 ± 0.9
Reflex amplitude (mm)	1.7 ± 0.5	1.8 ± 0.4
Reflex amplitude (%)	33 ± 7	34 ± 7
Before shivering		
Pupil diameter (mm)	2.6 ± 0.5*	2.6 ± 0.8*
Reflex amplitude (mm)	0.7 ± 0.2*	0.6 ± 0.2*
Reflex amplitude (%)	27 ± 6*	22 ± 5*
During shivering		
Pupil diameter (mm)	2.5 ± 0.3*	2.3 ± 0.5*
Reflex amplitude (mm)	0.6 ± 0.2*	0.4 ± 0.1*
Reflex amplitude (%)	26 ± 6*	18 ± 4*

Data are mean ± SD.

* Statistically significant differences from preinfusion values; none of the differences between meperidine and alfentanil was statistically significant. Plasma concentrations did not differ significantly over time.
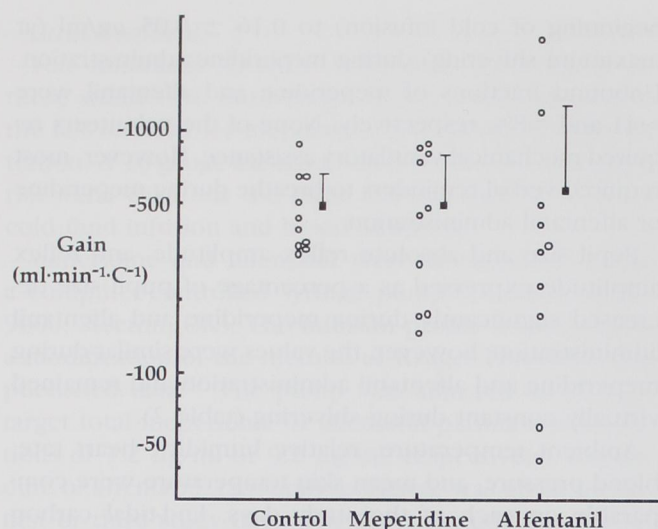
fentanil[5] each reduce the vasoconstriction and shivering thresholds comparably. These data suggest that the major cold defenses are similarly integrated and generally respond synchronously. The only apparent exception to this rule is meperidine, which reduces the shivering threshold nearly twice as much as the vasoconstriction threshold.[14]

Our hypothesis was that meperidine's special antishivering action might in part result from a reduction in the gain or maximum intensity of this response. However, our data failed to support either supposition, because both were well preserved. This result is consistent with those of the single other study evaluating the gain of shivering during anesthesia: Passias *et al.*[17] found that the gain of shivering was unchanged during administration of 30% nitrous oxide. We thus conclude that meperidine's special antishivering effect[6,7] is mediated by a disproportionate decrease in the shivering threshold,[14] rather than by a reduction in the gain or maximum intensity.

In our previous studies, we concluded that approximately equianalgesic concentrations of alfentanil[5] and meperidine[14] had been given in part because pupillary size and reflex amplitude were comparable with each drug. The alfentanil concentration was slightly less in our present volunteers than in our previous investigation,[5] and the pupils were slightly larger. Both results

Fig. 2. Individual gains of shivering (*open circles*), as determined by the slope of oxygen consumption *versus* core temperature regressions, on the control, meperidine, and alfentanil study days. Means are shown as filled squares, along with the associated standard deviations. There were no statistical differences among groups.

the difference was not statistically significant. The gains of shivering, as determined by oxygen consumption (fig. 2) and electromyography (fig. 3), were virtually identical on each day. The maximum shivering intensity was also similar with each opioid (table 3).

Normeperidine Protocol

None of the volunteers required mechanical ventilatory assistance, but most required verbal reminders to breathe during meperidine administration. Total plasma meperidine concentrations were essentially constant during the study (1.2 ± 0.1 µg/ml). In contrast, normeperidine concentrations increased significantly from 0.04 ± 0.01 µg/ml 1 h after starting administration to 0.28 ± 0.13 µg/ml 5 h after starting meperidine administration. Unbound fractions of meperidine and normeperidine were 42% and 36%, respectively. No shivering was observed clinically or electromyographically. Oxygen consumption did not increase significantly during the five study hours (fig. 4).

Discussion

The effects of volatile and intravenous anesthetics on cold responses in humans are reasonably characterized. Desflurane,[3] isoflurane,[2] propofol,[4] clonidine,[28] and al-
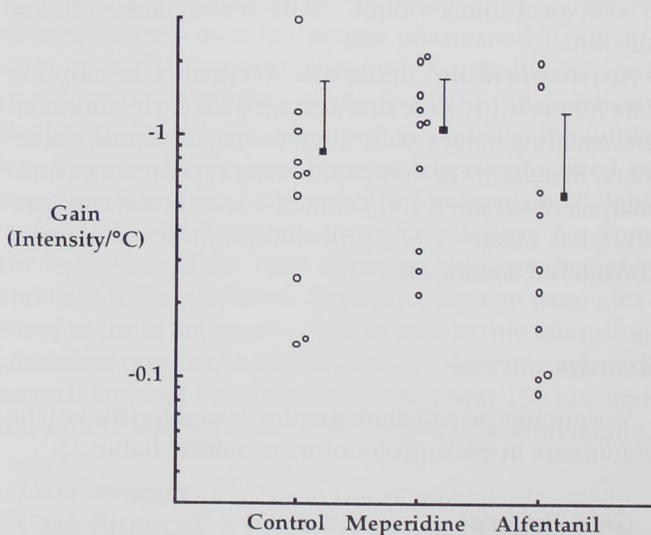

Fig. 3. Individual gains of shivering (*open circles*), as determined by the slope of electromyographic intensity *versus* core temperature regressions, on the control, meperidine, and alfentanil study days. Means are shown as filled squares, along with the associated standard deviations. There were no statistical differences among groups.

Table 3. Environmental, Hemodynamic, Respiratory, Fluid, and Thermoregulatory Data

	Control	Meperidine	Alfentanil
Ambient temperature (°C)	22.3 ± 1.2	22.4 ± 1.0	22.1 ± 0.7
Relative humidity (%)	42 ± 8	39 ± 11	39 ± 11
Mean arterial blood pressure (mmHg)	101 ± 9	103 ± 9	101 ± 8
Heart rate (beats/min)	62 ± 10	68 ± 11	62 ± 16
End-tidal P_{CO_2} (mmHg)	36 ± 3	42 ± 4*	42 ± 4*
Fluid volume (L)	2.3 ± 0.7	4.7 ± 1.3*	4.6 ± 1.6*
Mean skin temperature (°C)	31.1 ± 0.2	30.9 ± 0.1	31.0 ± 0.1
Shivering threshold (°C)	36.5 ± 0.4	34.8 ± 1.0*	35.2 ± 0.7*
Gain of shivering (ml·min^{-1}·°C^{-1})	−490 ± 182	−496 ± 300	−564 ± 721
Gain of shivering (intensity/°C)	−0.85 ± 0.83	−1.06 ± 0.68	−0.56 ± 0.68
Shivering maximum intensity (ml/min)	771 ± 117	777 ± 87	797 ± 142

Data are mean ± SD.

* Statistically significant difference from control.

suggest that the effective alfentanil concentration was somewhat less in the present study than in our previous one. The unbound meperidine concentration in our present study was slightly higher than in our previous study.[14] Pupillary size, however, was also larger. To the extent that pupil size correlates with analgesic ac-

Fig. 4. Total plasma meperidine concentrations were essentially constant (1.2 ± 0.1 μg/ml) during a 5-h infusion, started at elapsed time zero. In contrast, normeperidine concentrations increased significantly from 0.04 ± 0.01 μg/ml 1 h after starting administration to 0.28 ± 0.13 μg/ml 5 h after starting meperidine administration. Oxygen consumption did not increase significantly in these normothermic volunteers, indicating that normeperidine *per se* does not induce muscle rigidity or shivering.

tion,[26,29] it thus seems likely that our present volunteers experienced considerably less meperidine effect than did our previous ones, despite their having higher plasma concentrations.

The shivering threshold during alfentanil administration was ≈0.2°C less than in our previous study, after compensation for differences in unbound plasma concentration and skin temperature.[4,30] However, the shivering thresholds observed in our current volunteers were ≈0.8°C higher than those observed previously in volunteers given meperidine.[14] This relatively high shivering threshold during meperidine administration also is consistent with our current volunteers experiencing less opioid effect than would be predicted based on plasma concentration.

The shivering threshold in humans is slightly reduced by inspiration of 4% carbon dioxide.[31] The effect of hypercapnea on the gain of shivering remains unknown. The end-tidal carbon dioxide pressure in our volunteers was significantly higher when meperidine (42 ± 4 mmHg) or alfentanil (42 ± 4 mmHg) was administered than on the control day (36 ± 3 mmHg). However, all these values were within the normal clinical range and were thus unlikely to have influenced very much the observed thermoregulatory responses.

Development of tolerance is both dose and time dependent, but is similar to opioids of differing potencies.[32] The time required for opioid-naive humans to recover normal pharmacodynamic responses after several hours of narcotic administration remains unclear. However, it seems likely that the 2 weeks we allowed between meperidine and alfentanil administration was adequate.[22] Acute tolerance can develop within hours
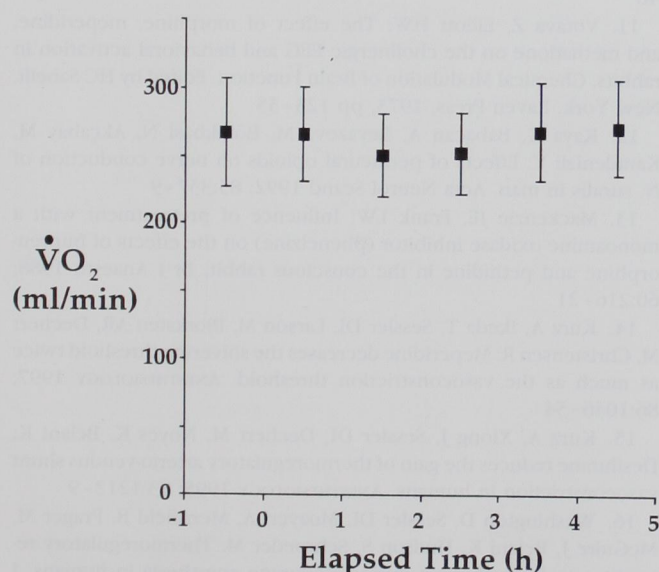
in animals,[32] but it remains unknown whether tolerance develops equally rapidly in humans. We used pupillary responses to evaluate opioid effect. As expected, pupillary responses were markedly reduced by opioid administration.[26] However, pupillary responses were comparable at the two measurement points on each study day. These results suggest that acute tolerance did not decrease opioid effect for the hours required for the test.

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 thus were significantly greater at maximum shivering than at the beginning of the cooling infusion, although the levels never exceeded 10% of the total plasma concentration of meperidine. High concentrations of normeperidine can cause seizures,[18,19] but the drug probably has weak opioid properties. Furthermore, pupillary responses were comparable at the beginning and end of the drug infusion, despite the progressive increase in the normeperidine concentration. It therefore seems unlikely that normeperidine has substantial thermoregulatory consequences. Consistent with this theory, we failed to observe clinical shivering or muscle rigidity, or any significant increase in oxygen consumption during prolonged meperidine administration that increased plasma normeperidine concentration to 0.28 ± 0.13 μg/ml (23% of meperidine concentration). It is thus unlikely that the gain of shivering, as determined in the first protocol, was influenced by the inevitable accumulation of normeperidine.

In conclusion, although meperidine and alfentanil administration significantly decreased the shivering threshold, neither meperidine nor alfentanil reduced the gain and the maximum intensity of shivering. These results suggest that meperidine's special antishivering effect is primarily mediated by a disproportionately large reduction in the shivering threshold.

References

1. Sessler DI: Perioperative hypothermia. N Engl J Med 1997; 336:1730–7

2. Xiong J, Kurz A, Sessler DI, Plattner O, Christensen R, Dechert M, Ikeda T: Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1996; 85:240–5

3. Annadata RS, Sessler DI, Tayefeh F, Kurz A, Dechert M: Desflurane slightly increases the sweating threshold, but produces marked, non-linear decreases in the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 83:1205–11

4. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 82:1169–80

5. Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1995; 83:293–9

6. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. J Cardiothorac Vasc Anesth 1987; 1:24–8

7. Pauca AL, Savage RT, Simpson S, Roy RC: Effect of pethidine, fentanyl and morphine on post-operative shivering in man. Acta Anaesthesiol Scand 1984; 28:138–43

8. Kurz M, Belani K, Sessler DI, Kurz A, Larson M, Blanchard D, Schroeder M: Naloxone, meperidine, and shivering. ANESTHESIOLOGY 1993; 79:1193–201

9. Helgesen KT, Ellingsen Ø, Ilebekk A: Inotropic effect of meperidine: Influence of receptor and ion channel blockers in the rat atrium. Anesth Analg 1990; 70:499–506

10. Wynn RL, Bergman SA, Rudo FG, Leventer M: GABA mimetics diminish antinociception of meperidine under conditions which enhance other opioid μ-agonists. Arch Int Pharmacodyn 1990; 304:136–46

11. Votava Z, Elliott HW: The effect of morphine, meperidine, and methadone on the cholinergic EEG and behavioral activation in rabbits, Chemical Modulation of Brain Function. Edited by HC Sabelli. New York, Raven Press, 1973, pp 123–35

12. Kaya K, Babacan A, Beyazova M, Bölükbasi N, Akçabay M, Karadenizli Y: Effects of perineural opioids on nerve conduction of N. suralis in man. Acta Neurol Scand 1992; 85:337–9

13. Mackenzie JE, Frank LW: Influence of pretreatment with a monoamine oxidase inhibitor (phenelzine) on the effects of buprenorphine and pethidine in the conscious rabbit. Br J Anaesth 1988; 60:216–21

14. Kurz A, Ikeda T, Sessler DI, Larson M, Bjorksten AR, Dechert M, Christensen R: Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. ANESTHESIOLOGY 1997; 86:1046–54

15. Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K: Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans. ANESTHESIOLOGY 1995; 83:1212–9

16. Washington D, Sessler DI, Moayeri A, Merrifield B, Prager M, McGuire J, Belani K, Hudson S, Schroeder M: Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. J Appl Physiol 1993; 74:82–7

17. Passias TC, Mekjavic IB, Eiken O: The effect of 30% nitrous oxide on thermoregulatory responses in humans during hypothermia. ANESTHESIOLOGY 1992; 76:550–9

18. Goetting MG: Neurotoxicity of meperidine. Ann Emerg Med 1985; 14:1007–9

19. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidberg MM: Accumulation of normeperidine, an active metabolite of meperi-

dine in patients with renal failure and cancer. Ann Intern Med 1977; 86:738–41

20. Crankshaw DP, Edward NE, Blackman GL, Boyd MD, Chan HNJ, Morgan DJ: Evaluation of infusion regimens for thiopentone as a primary anaesthetic agent. Eur J Clin Pharmacol 1985; 28:543–52

21. Scott JC, Ponganis KV, Stanski DR: EEG quantification of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. ANESTHESIOLOGY 1985; 62:234–41

22. Carter BD, Medzihradsky F: Receptor mechanisms of opioid tolerance in SH-SY5Y human neural cells. Mol Pharmacol 1993; 43:465–73

23. Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. ANESTHESIOLOGY 1994; 80:780–8

24. Sessler DI, McGuire J, Moayeri A, Hynson J: Isoflurane-induced vasodilation minimally increases cutaneous heat loss. ANESTHESIOLOGY 1991; 74:226–32

25. Kim J-S, Ikeda T, Sessler D, Turakhia M, Jeffrey R: Epidural anesthesia reduces the gain and maximum intensity of shivering. ANESTHESIOLOGY 1998; 88:851–7

26. Martin WR: Pharmacology of opioids. Pharmacol Rev 1983; 35:283–323

27. Larson M, Tayefeh F, Sessler DI, Daniel M, Noorani M: The sympathetic nervous system does not mediate pupillary dilation to noxious stimulation during desflurane anesthesia. ANESTHESIOLOGY 1996; 85:748–54

28. Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI: Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. ANESTHESIOLOGY 1993; 79:470–4

29. Jasinski DR: Assessment of the abuse potentiality of morphinelike drugs (methods used in man), Drug Addiction 1: Morphine, Sedative/hypnotic and Alcohol Dependence. Edited by WR Martin. Berlin, Springer-Verlag, 1977, pp 197–258

30. Cheng C, Matsukawa T, Sessler DI, Kurz A, Merrifield B, Lin H, Olofsson P: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. ANESTHESIOLOGY 1995; 82:1160–8

31. Johnston CE, Elias DA, Ready AE, Giesbrecht GG: Hypercapnia lowers the shivering threshold and increases core cooling rate in humans. Aviat Space Environ Med 1996; 67:438–44

32. Kissin I, Brown PT, Robinson A, Bradley EL: Acute tolerance in morphine analgesia: Continuous infusion and single injection in rats. ANESTHESIOLOGY 1991; 74:166–71