

## Naloxone, Meperidine, and Shivering

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**Background:** Meperidine, which binds both  $\mu$  and  $\kappa$  opioid receptors, is reportedly more effective in treating shivering than are equianalgesic doses of morphine (a nearly pure  $\mu$ -receptor agonist). Furthermore, butorphanol, a  $\kappa$ -receptor agonist/antagonist, treats shivering better than does fentanyl, which mostly binds  $\mu$  receptors. These data indicate that much of meperidine's special antishivering activity may be mediated by its  $\kappa$  activity. Accordingly, the authors tested the hypothesis that the antishivering activity of meperidine will be minimally impaired by low-dose naloxone (blocking most  $\mu$ -receptors), but largely prevented by high-dose naloxone (blocking all  $\mu$  and most  $\kappa$  receptors).

**Methods:** Twelve volunteers each participated on 2 days. On both days, shivering was induced by central venous infusion of cold fluid. Twenty minutes later, six volunteers were given a placebo infusion of saline on one day, or an infusion of 0.5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  naloxone hydrochloride ("low-dose," designed to block  $\mu$  receptors) on the other. The second group of six volunteers was given a saline bolus and infusion on one day, or a bolus of 11.5  $\mu\text{g}/\text{kg}$  naloxone hydrochloride followed by an infusion of naloxone at 5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ("high-dose," designed to block both  $\mu$  and  $\kappa$  receptors) on the other day. The

infusions were continued for the duration of the study. The order of the treatment days (saline *vs.* naloxone) was randomly assigned, and the study was double blinded. Fifteen minutes after the test infusion was started, all 12 volunteers were given an intravenous bolus of 1 mg/kg meperidine hydrochloride. Pupillary diameter and light reflex amplitude were used to quantify opioid-receptor agonist activity; shivering intensity was evaluated using oxygen consumption.

**Results:** Administration of naloxone alone did not alter oxygen consumption, pupil size, or the pupillary light reflex. No pupillary constriction was detected in either group when naloxone and meperidine were combined; in contrast, meperidine alone decreased pupil size and amplitude of the light reflex 30%. The meperidine bolus decreased oxygen consumption nearly to control values when the volunteers were given saline placebo. Combined administration of meperidine and low-dose naloxone also significantly reduced oxygen consumption, but the reduction and the duration of the reduction was less than during saline. When the volunteers were given high-dose naloxone, meperidine only slightly reduced oxygen consumption, and the values rapidly returned to premeperidine levels.

**Conclusions:** These data indicate that the antishivering property of meperidine is not fully mediated by  $\mu$ -receptors. Although meperidine has well-known nonopioid actions, stimulation of  $\kappa$  receptors seems a likely alternative explanation for much of the drug's antishivering action. (Key words: Analgesics, opioids: meperidine. Antagonists, opioid: naloxone. Brain: hypothalamus. Temperature: hypothermia. Thermoregulation: setpoint; shivering; threshold.)

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THE opioid-receptor agonist meperidine has a high affinity for  $\mu$  receptors, and a moderate affinity for  $\kappa$  and  $\delta$  receptors.<sup>1</sup> Most studies conclude that meperidine is considerably more effective in treating shivering than are equianalgesic doses of relatively pure  $\mu$ -receptor agonists, such as morphine and fentanyl.<sup>2,3</sup> Similarly, butorphanol (a  $\kappa$ -receptor agonist/antagonist) stops shivering better than does fentanyl.<sup>4</sup> These data indicate that  $\kappa$ -receptor stimulation may contribute to meperidine's antishivering action. Additional support for this theory comes from the observation that cold-induced shivering, blocked by meperidine administration, returns to its previous intensity after high-dose naloxone administration.<sup>5</sup>

Antishivering efficacy *not* mediated by  $\mu$  receptors should remain intact when  $\mu$  receptors are blocked by

relatively low-dose naloxone administration. In contrast, high-dose naloxone will block both  $\mu$  and  $\kappa$  receptors, leaving intact only nonopioid actions of meperidine.<sup>6</sup> Accordingly, we tested the hypothesis that the antishivering activity of meperidine will be minimally impaired by low-dose naloxone (blocking most  $\mu$ -receptors), but largely prevented by high-dose naloxone (blocking all  $\mu$  and most  $\kappa$  receptors). We confirmed that both doses of naloxone blocked  $\mu$  receptors by measuring pupil size and the amplitude of the pupillary light reflex.

### Materials and Methods

After approval of the University of California, San Francisco Committee on Human Research, we studied 12 healthy volunteers. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. Volunteers refrained from coffee and tea intake during the 8 h before the investigations. Six volunteers were initially studied, using a relatively low dose of naloxone; the remaining six volunteers were evaluated subsequently, during high-dose naloxone administration.

#### Protocol

Each volunteer participated on 2 consecutive days. On each, shivering was induced by central venous infusion of cold lactated Ringer's solution. The volunteers then were given an infusion of saline placebo on 1 day, and low- or high-dose naloxone on the other. Fifteen minutes after starting the test infusion, all volunteers were given an intravenous bolus of 1 mg/kg meperidine.

During the study, minimally clothed volunteers reclined on a standard operating room table. A 16-G catheter was placed into the superior vena cava *via* the internal jugular vein using standard technique. After 5 min of control measurements, lactated Ringer's solution at  $\approx 3^\circ\text{C}$  was infused into the central catheter at  $1.5\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 5 min, and then at  $1.0\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for an additional 55 min. Lactated Ringer's solution was cooled by passing it through an aluminum cardiopulmonary bypass heat exchanger immersed in an ice and salt-water slurry. We have previously described this technique, and its thermoregulatory consequences.<sup>7</sup>

Twenty minutes after the cold lactated Ringer's infusion was begun, the test infusion was started. In the

initial study, volunteers were given an intravenous saline placebo or an infusion of  $0.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  naloxone hydrochloride (Elkins-Sinn, Cherry Hill, NJ). This infusion, "low-dose," was designed to block most  $\mu$  receptors. The second six volunteers were given saline or a bolus of  $11.5\text{ }\mu\text{g}/\text{kg}$  naloxone hydrochloride followed by an infusion of naloxone at  $5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ("high-dose," designed to block all  $\mu$  and most  $\kappa$  receptors). The naloxone dose was increased  $\approx 10$ -fold in the second trial because the  $\mu/\kappa$  receptor binding ratio is  $\approx 10$ .<sup>1,8</sup> Furthermore, the naloxone dose required to block the action of ethylketazocine (a  $\kappa$ -receptor agonist) in rats is ten times that required to block the effects of morphine (a nearly pure  $\mu$ -receptor agonist,<sup>6</sup> indicating that drug lipid solubility has not confounded interpretation of the receptor-binding data.<sup>9</sup>

The order of the treatment days (saline *vs.* naloxone) was randomly assigned, and drug administration was double-blinded; the test infusions were continued for the duration of the study. Fifteen minutes after the test infusion was started, all volunteers were given an intravenous bolus of 1 mg/kg meperidine hydrochloride.

In preliminary studies, we noticed a strong placebo effect: volunteers, who were *unaware* of the drug being given, would report a variety of sensations when saline, naloxone, and meperidine were administered. However, the sensations were not consistently related to the administered drug. Consequently, we found it necessary not only to continue administering naloxone in a double-blinded fashion, but to avoid informing the volunteers what sensations they might experience and when boluses and infusions were started.

#### Measurements

The electrocardiogram and oxyhemoglobin saturation ( $S_pO_2$ ) were monitored continuously and blood pressure was determined oscillometrically at 5-min intervals by monitors integrated into a Modulus CD Anesthesia System (Ohmeda Corp., Liberty Corner, NJ). These data were recorded using IdaCare (Hermes System, Belgium), which is a Macintosh-based (Apple Computer, Cupertino, CA) patient information management software. Body fat was measured using infrared interactance (Futrex 1000, Futrex, Hagerstown, MD).<sup>10</sup>

Ambient temperatures were recorded from a thermocouple positioned at the level of the operating room table, but well away from any heat-producing equipment. Core temperatures were measured using dispos-

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able thermocouple probes (Mallinckrodt Anesthesia Products, St. Louis, MO) positioned in contact with the tympanic membrane.

The thermocouples were connected to a calibrated Iso-Thermex electronic thermometer (Columbus Instruments, Columbus, OH) having an accuracy of  $0.1^{\circ}\text{C}$  and a precision of  $0.01^{\circ}\text{C}$ . Temperature recordings began 5 min before administration of the lactated Ringer's solution, and continued at 5-min intervals until 20 min after meperidine was given. Finger vasoconstriction was evaluated using the forearm minus fingertip, skin-temperature gradient<sup>11</sup>; values exceeding  $4^{\circ}\text{C}$  indicate significant vasoconstriction. Ambient relative humidity was measured by a Model HX93 humidity transmitter (Omega Engineering, Stamford, CT).

Pupillary diameter and light reflex amplitude were evaluated using a portable infrared pupillometer (Applied Sciences Laboratory, Waltham, MA) having a resolution of 0.1 mm. The instrument was programmed to search for a stable pupillary diameter, flash a 0.5-s light stimulus, and initiate a 2-s-long, 10-Hz scan at the start of the stimulus. The light stimulus is provided by two green, light-emitting diodes having a combined intensity of 130 candelas/m<sup>2</sup>. Measurements were made with ambient light set to approximately 150 lux. To ensure a consistent visual fixation point, the volunteers focused on the eye of the examiner during each scan, at a distance of approximately 50 cm. All measurements were taken from the right eye. Ambient light was excluded from the left eye by an opaque bandage. We have previously described this technique in detail.<sup>12</sup>

Clinical experience has shown that three scans are sufficient in most volunteers to record a reproducible reflex pattern. We, therefore, recorded at least three sets of data to produce one averaged scan from which pupil size and reflex amplitude were calculated. The difference between the prestimulus diameter and the minimum diameter in the 2 s after the stimulus was defined as the reflex amplitude.

Shivering was evaluated using whole-body oxygen consumption. The six volunteers in the initial study group (low-dose) inspired room air *via* a tightly fitted face mask with an integral one-way valve (Hans Rudolph, Kansas City, MO). Expiratory volume was measured by a water-sealed respirometer, and mixed expired oxygen concentration was determined using a calibrated mass spectrometer (Medspect, St. Louis, Missouri). Oxygen consumption was calculated from inspiratory oxygen concentration and expiratory volume and oxygen concentration.

In the remaining six volunteers (high-dose), oxygen consumption was measured with a Deltatrac<sup>TM</sup> metabolic monitor (SensorMedics, Yorba Linda, CA). The monitor measures the oxygen concentration in exhaust gas drawn at a constant flow of 40 l/min through a clear plastic canopy placed over the volunteer's head. Oxygen consumption is determined from the difference in oxygen content between the mixed exhaust gas and the inspired room air. Measurements were averaged over 1-min intervals, and were recorded three times in each 5-min interval. Oxygen consumption values in both groups are reported dry, at standard temperature and pressure, and normalized to the weight of the volunteers.

#### Statistical Analysis

As recommended by Matthews *et al.*, within-group data were statistically analyzed only at a limited number of pertinent times.<sup>13</sup> Within-group data were analyzed using repeated-measures ANOVA, with Dunnett's test for comparison to control (precooling) values. Differences between the three treatment groups were evaluated using one-way ANOVA and Scheffé's S tests. Results are presented as means  $\pm$  SD; differences were considered statistically significant when  $P < 0.05$ . The six volunteers in each group responded similarly to saline infusion; consequently, these data were grouped for purposes of comparison.

#### Results

Ambient temperatures averaged  $23.2 \pm 0.9^{\circ}\text{C}$ , and ambient relative humidity averaged  $54 \pm 4\%$ , during the study period; these values were comparable on the naloxone and saline study days and in the low-dose and high-dose groups. All volunteers were intensely vasoconstricted on both study days, the forearm skin-temperature gradient exceeding  $4^{\circ}\text{C}$  throughout. There were no significant differences in the morphometric characteristics of the two groups (table 1).

Core temperature changes were similar in the low-dose and high-dose groups, and on the saline and naloxone treatment days. Tympanic membrane temperatures decreased  $\approx 1^{\circ}\text{C}$  during the first 15 min of lactated Ringer's administration, then remained nearly constant for 20 min, and subsequently decreased an additional  $\approx 0.5^{\circ}\text{C}$ .

Induction of core hypothermia and shivering did not significantly alter pupil size or reflex amplitude; low-

**Table 1. Morphometric Characteristics**

Group	Age (yr)	Weight (kg)	Height (cm)	Body Fat (%)	Gender (number female)
Low-dose	27 ± 5	72 ± 12	174 ± 14	22 ± 7	2
High-dose	25 ± 3	63 ± 7	175 ± 5	18 ± 5	3

Data except in last column are means ± SD.

There were no statistically significant differences between the groups.

dose and high-dose naloxone administration had little further effect. Concurrent meperidine and naloxone administration slightly increased pupillary diameter  $\approx 0.5$  mm in both the low- and high-dose naloxone groups, but did not increase the reflex amplitude. In contrast, when meperidine was given without naloxone, pupil size decreased  $\approx 1.4$  mm, and the reflex amplitude decreased  $\approx 0.75$  mm in each group. The percentage changes are shown in figure 1 and table 2.

In both groups, oxygen consumption increased two- to threefold after the lactated Ringer's infusion was started, and administration of naloxone (low- or high-dose) and saline did not alter the response. During the saline infusion, oxygen consumption returned to nearly control values within  $\approx 10$  min after the meperidine bolus, and began to recover only near the end of the study. During low-dose naloxone administration, the meperidine bolus decreased oxygen consumption less than during saline, and shivering recurred more rapidly. Oxygen consumption decreased only slightly when meperidine was given during the high-dose naloxone infusion, and rapidly returned to its previous intensity (fig. 2, table 3).

## Discussion

Postanesthetic shivering-like tremor is associated with increases in metabolic rate, surgical pain, and intracranial and intraocular pressures. Although postanesthetic tremor contains abnormal clonic components, most of the tremor resembles normal shivering.<sup>14</sup> Furthermore, both components are thermoregulatory; that is, preceded by core hypothermia and peripheral vasoconstriction. Optimal intraoperative thermal management is, thus, to maintain normothermia in most patients. Doing so not only will prevent nearly all postoperative shivering,<sup>15</sup> but will, as well, prevent other complications of hypothermia, including prolonged drug action,<sup>16</sup> negative nitrogen balance,<sup>17</sup> impaired

coagulation,<sup>18</sup> and decreased resistance to wound infections.<sup>19</sup>

Nonetheless, shivering may occur in patients who unavoidably become hypothermic, or in those deliberately kept hypothermic to minimize risk of ischemia, hypoxemia, or malignant hyperthermia.<sup>20-24</sup> Furthermore, shivering may occur in normothermic patients developing a centrally mediated fever in response to hypothermic cardiopulmonary bypass, mismatched blood transfusions, blood in the fourth cerebral ventricle, or certain drugs.

As expected from our previous studies,<sup>12</sup> hypothermia and shivering only slightly reduced pupillary size and reflex amplitude. The observed gradual decreases in pupil size during cooling may result from adaptation by the volunteers to the process of pupillary measurements,<sup>25</sup> or gradual cooling of the iris.<sup>26</sup> Our data confirm that naloxone alone, even in large doses, has no effect on the human pupil.<sup>8</sup>

A crucial facet of our argument is that the absence of pupillary constriction after combined low-dose naloxone and meperidine administration confirms effective antagonism of central  $\mu$  receptors. The human pupil is exquisitely sensitive to  $\mu$ -receptor agonists.<sup>8,25</sup> For example, miosis persists at plasma concentrations producing no discernible respiratory depression or analgesia.<sup>27</sup> Similarly, heroin-induced miosis recovers before other subjective and objective opiate receptor-agonist effects during dissipation of naltrexone antagonism.<sup>28</sup> Consistent with this sensitivity, pupils remained constricted after shivering returned to its initial intensity when the volunteers were given meperidine/saline.

It may be argued that the absence of pupillary constriction after combined naloxone/meperidine administration represented a composite of two separate and opposing effects, specifically, an opioid action causing constriction and an anticholinergic effect producing dilation. This explanation is unlikely for two reasons. First, the magnitude of pupillary constriction that we

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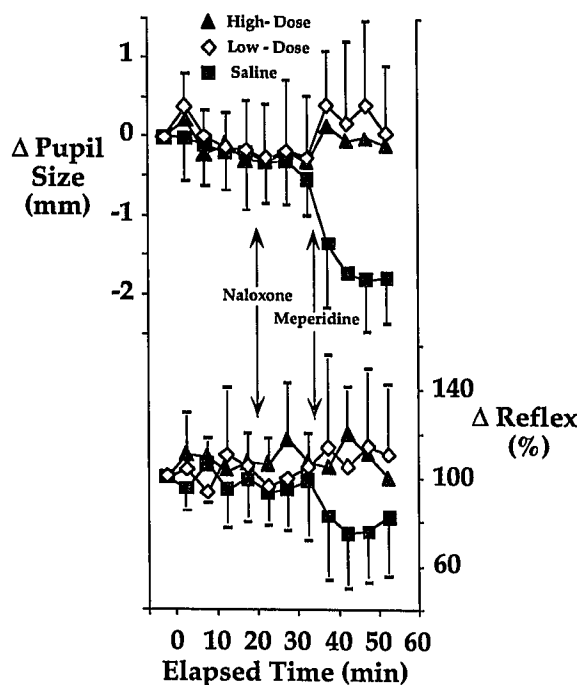


Fig. 1. After 5 min of control measurements ( $-5$  to  $0$  elapsed min), lactated Ringer's solution at  $\approx 3^{\circ}\text{C}$  was infused into the internal jugular vein at  $1.5\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 5 min, and then at  $1.0\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for the remainder of the study. Twelve volunteers were given saline as the test infusion, started at 20 elapsed min. On a second study day, six volunteers were given naloxone hydrochloride  $0.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (low-dose), and six others were given naloxone hydrochloride  $11.5\text{ }\mu\text{g}/\text{kg}$  bolus followed by an infusion of  $5.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (high-dose). All volunteers were given a  $1\text{-mg}/\text{kg}$  bolus of meperidine hydrochloride at 35 elapsed min. Initial pupil size was  $\approx 5$  mm, and initial reflex amplitude was  $\approx 2$  mm during each treatment. Induction of core hypothermia and administration of the test solution had little effect on pupil size or reflex amplitude. Meperidine administration combined with either dose of naloxone had little effect on reflex amplitude, but increased pupil size  $\approx 0.5$  mm. In contrast, meperidine infusion without concurrent naloxone administration significantly decreased pupil size  $\approx 30\%$  and reflex amplitude  $\approx 0.75$  mm. See table 2 for statistic analysis.

observed after meperidine/saline administration was comparable to that produced by equianalgesic doses of predominantly  $\mu$ -receptor agonists, such as morphine and alfentanil.<sup>8,25</sup> Thus, the atropine-like effects of meperidine were insufficient to significantly oppose the constriction produced by its dominant  $\mu$ -receptor agonist effect. Secondly, anticholinergic drugs not only dilate the pupil, but also decrease the light reflex by antagonizing muscarinic receptors controlling the pupillary sphincter.<sup>29</sup> However, the small pupillary dilation that we observed after combined naloxone/me-

peridine administration was not associated with a decreased light reflex amplitude. Most likely, the dilation reflected a mild general central nervous system activation, perhaps mediated by meperidine's central anticholinergic action.<sup>30</sup> Although stimulation of  $\kappa$  receptors has been shown to produce miosis in dogs,<sup>31</sup> a similar constriction has not been reported in humans. Instead, the miotic effects of pentazocine, a mixed  $\mu/\kappa$  agonist, are blocked by a dose of naltrexone thought to selectively block the  $\mu$  receptor.<sup>32</sup>

Postanesthetic shivering can be treated pharmacologically or by warming the skin surface. Cutaneous heating treats shivering by increasing thermal input from the skin, which compensates for a degree of core hypothermia.<sup>33</sup> Consequently, this technique is effective, even in patients with reduced core temperatures. Alternatively, a variety of drugs, including ketanserin,<sup>34,35</sup> clonidine,<sup>35-37</sup> methylphenidate,<sup>38</sup> cholinomimetics,<sup>39</sup> and taurine,<sup>40</sup> have proven to be effective treatments for both normal cold-induced shivering and postanesthetic shivering. But perhaps the most frequently used pharmacologic treatment is the opioid meperidine.

Administration of  $\mu$ -receptor agonists to animals produces a variety of species-specific thermoregulatory effects, but, perhaps, most typically, hyperthermia at low doses and hypothermia at higher doses.<sup>41</sup> The thermoregulatory effects of such opioids in humans remain unclear, but certainly they do not routinely produce hyperthermia. Data from opioid investigations in animals, therefore, should be extrapolated to humans only with great caution.

The thermoregulatory effects of opioids have not been fully evaluated in humans. Nitrous oxide combined with fentanyl significantly decreases the threshold for vasoconstriction in humans.<sup>42</sup> However, the independent effects of fentanyl cannot be determined from this study, because nitrous oxide alone also decreases thermoregulatory thresholds.<sup>43-45</sup> Nonetheless,  $\mu$ -agonist opioids probably do impair thermoregulatory control in humans, either by increasing the interthreshold range, as do general anesthetics,<sup>46</sup> or by decreasing the setpoint.<sup>41</sup>

To the extent that  $\mu$ -agonist opioids, as a class, impair thermoregulation and cold-induced shivering in humans,<sup>38,47</sup> meperidine will also. Thus, meperidine's ability to treat shivering probably results, at least in part, from thermoregulatory impairment mediated by  $\mu$  receptors. Our results are consistent with this theory: the antishivering action of meperidine was somewhat

Table 2. Pupil Size and Light Reflex at Specific Study Phases

Group	Prenaloxone or Placebo	Premeperidine	Lowest Postmeperidine	End
Size (mm)				
Placebo	-0.2 ± 0.7	-0.5 ± 0.5*	-2.1 ± 0.6*	-1.8 ± 0.6*
Low-dose	-0.2 ± 0.6	-0.3 ± 0.8	0.0 ± 0.9†	0.0 ± 0.8†
High-dose	-0.3 ± 0.3	-0.3 ± 0.6	-0.3 ± 0.5†	-0.2 ± 0.5†
Reflex (%)				
Placebo	100 ± 20	83 ± 29	69 ± 24*	82 ± 27
Low-dose	105 ± 27	105 ± 32	103 ± 31†	110 ± 32
High-dose	107 ± 13	107 ± 13	98 ± 14†	100 ± 16

Data are means ± SD.

Changes from the control value are shown during the prenaloxone or placebo (0–20 min) and premeperidine (20–35 min) periods. The lowest postmeperidine value shows the minimum value recorded after meperidine administration (usually within 10 min of administration). The last column shows values recorded at the end of the study (50–55 min).

\*  $P \leq 0.05$  versus control.

†  $P \leq 0.05$  versus saline.

impaired by administration of low-dose naloxone. Presumably, differing responses during saline and low-dose naloxone administration result from  $\mu$ -receptor-mediated general thermoregulatory impairment.

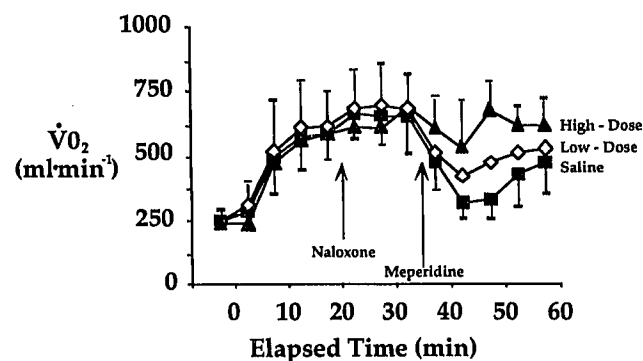


Fig. 2. After 5 min of control measurements (–5 to 0 elapsed min), lactated Ringer's solution at  $\approx 3^{\circ}\text{C}$  was infused into the internal jugular vein at  $1.5\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for 5 min, and then at  $1.0\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  for the remainder of the study. Twelve volunteers were given saline as the test infusion, started at 20 elapsed min. On a second study day, six volunteers were given naloxone hydrochloride  $0.5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (low-dose), and six others were given naloxone hydrochloride  $11.5\text{ }\mu\text{g}/\text{kg}$  bolus followed by an infusion of  $5.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (high-dose). All volunteers were given a  $1\text{-mg}/\text{kg}$  bolus of meperidine hydrochloride at 35 elapsed min. Lactated Ringer's infusion increased oxygen consumption  $\approx 3$ -fold, and oxygen consumption was not further altered by naloxone or saline administration. Meperidine combined with saline returned oxygen consumption to nearly baseline values. Oxygen consumption decreased somewhat less during low-dose naloxone infusion, and least when the volunteers were given high-dose naloxone. Nonetheless, the maximum decrease in the immediate postmeperidine period was comparable in the three groups. See table 3 for statistic analysis.

Considerable antishivering activity (as indicated by reduction of oxygen consumption) remained, however, when meperidine was combined with low-dose naloxone, indicating that the antishivering effect of meperidine is not mediated exclusively by  $\mu$  receptors. In distinct contrast, the antishivering action of meperidine was decreased substantially by simultaneous infusion of high-dose naloxone. The most likely explanation for the differing inhibition during low- and high-dose naloxone is that  $\kappa$ -receptor (or possibly  $\delta$ -receptor) binding also contributes to the antishivering effect of meperidine. Thus, the antishivering effect of meperidine was only partially blocked by the lower dose of naloxone (which blocked  $\mu$  receptors), but was almost completely prevented by the high-dose infusion that was designed to block both  $\mu$  and  $\kappa$  receptors.

Consistent with this explanation, butorphanol (a  $\kappa$ -receptor agonist/antagonist) stops shivering better than fentanyl.<sup>4</sup> Similarly, cold-induced shivering, blocked by meperidine administration, returns to its previous intensity after high-dose naloxone administration.<sup>5</sup> An apparent antishivering effect of  $\kappa$  receptors (most of which are located in the spinal cord) is intriguing because shivering, more than other thermoregulatory responses, may be controlled at the level of the spinal cord.<sup>48–50</sup>

Although high-dose naloxone blocked most of the antishivering action of meperidine, some inhibition persisted even when the volunteers were given  $\approx 15\text{ mg}$  of naloxone. Most likely, persistent inhibition resulted from an incomplete block of  $\kappa$  receptors. But

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Table 3. Oxygen Consumption at Specific Study Phases

Group	Oxygen Consumption (ml/min)					Time (min) to 150% Increase in Oxygen Consumption
	Control	Prenaloxone or Placebo	Premeperidine	Lowest Postmeperidine	End	
Saline	247 ± 30	605 ± 78*	632 ± 98*	268 ± 53	455 ± 124*	12.5 ± 5
Low-dose	233 ± 35	600 ± 126*	719 ± 208*	331 ± 90	488 ± 156*	8 ± 6
High-dose	235 ± 34	585 ± 65*	688 ± 62*	427 ± 137*†	616 ± 110*	2 ± 2

Average ( $\pm$ SD) values are presented for the control ( $-5-0$  min), prenaloxone ( $0-20$  min), and premeperidine periods ( $20-35$  min). The fifth column shows the minimum value recorded after meperidine administration (usually within 10 min of administration). The sixth column shows values recorded at the end of the study. The last column shows the time required for oxygen consumption to increase to 150% of its lowest postmeperidine value; the times differed significantly during each of the treatments.

\*  $P \leq 0.05$  versus control.

†  $P \leq 0.05$  versus saline.

an alternative explanation is that some of meperidine's antishivering activity is not mediated by either opioid receptor. Consistent with this possibility, meperidine is known to possess numerous nonopioid actions.

Unlike other opioids, meperidine administration produces generalized electroencephalographic (EEG) activation, apparently *via* inhibition of central cholinergic receptors.<sup>30</sup> Monoamine oxidase inhibitors combined with meperidine, but not other opioids, produces a potentially lethal hyperthermia syndrome.<sup>51</sup>  $\tau$ -Amino butyric acid (GABA)-mimetic drugs reduce the antinociceptive effect of meperidine, but enhance the potency of fentanyl.<sup>52</sup> Unlike other opioids, which have no direct effect on the heart or are cardiodepressive, meperidine has a positive inotropic action not prevented by  $\mu$ -receptor antagonists,  $\alpha$ - or  $\beta$ -blockers, histamine blockers, calcium channel blockers, or fast sodium-channel blockers.<sup>53</sup> And finally, meperidine, but not morphine or fentanyl, has local anesthetic properties.<sup>54</sup>

The best-known nonopioid effect of meperidine is its central anticholinergic action.<sup>30</sup> (Fentanyl also has an antimuscarinic action.<sup>55</sup>) However, hypothalamic application of acetylcholine produces a dose-dependent, atropine-blocked *decrease* in set point<sup>41</sup>; furthermore, postanesthetic shivering in mice is prevented by administration of central muscarinic or nicotinic agonists.<sup>39</sup> It is, thus, unlikely that an anticholinergic drug would prevent shivering.

We made no attempt to determine plasma meperidine or naloxone concentrations. Instead, we used pupillary responses to document the  $\mu$ -receptor action of administered meperidine, and its inhibition by naloxone. In addition, even the "low-dose" of naloxone was quite

large by clinical standards. Before the meperidine bolus, these volunteers were given  $\approx 500$   $\mu$ g of naloxone; subsequently, they were given an additional  $\approx 700$   $\mu$ g. Even a fraction of this dose typically would be sufficient to fully arouse an apneic and unconscious opioid overdose victim.

Core temperature decreased only  $\approx 1^\circ$  C during our study. Nonetheless, rapid infusion of iced lactated Ringer's solution produced a severe and ongoing cold stress, one requiring the volunteers to shiver vigorously to prevent additional hypothermia. Thus, while  $\approx 0.5$  mg/kg of meperidine typically is sufficient to treat normal or postanesthetic shivering,<sup>2</sup> our volunteers required more. In preliminary investigations, we determined that 1 mg/kg reliably arrested the shivering, yet allowed some recovery during the study. We consider reemergence of shivering to be a critical feature of this protocol, because it allows us to distinguish among responses to the three treatments. It is likely that results would have been similar had we infused lactated Ringer's solution at a lower rate and given less meperidine.

These data indicate that the antishivering property of meperidine is not fully mediated by  $\mu$ -receptors. Although meperidine has well-known nonopioid actions, stimulation of  $\kappa$  receptors seems a likely alternative explanation for much of the drug's antishivering action.

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