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# The Effects of Meperidine and Sufentanil on the Shivering Threshold in Postoperative Patients

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***Background:*** **Meperidine (pethidine) reportedly treats postoperative shivering better than equianalgesic doses of other μ-receptor agonists. The authors' first goal was to develop a method to accurately determine postoperative shivering thresholds, and then to determine the extent to which meperidine and sufentanil inhibit postoperative shivering.**

***Methods:*** **A computer-controlled infusion was started before operation in 30 patients, with target plasma concentrations of 0.15, 0.30, or 0.60 μg/ml meperidine or 0.1, 0.15, or 0.2 ng/ml sufentanil targeted; patients were randomly assigned to each drug and concentration. The infusion was continued throughout surgery and recovery. Anesthesia was maintained with nitrous oxide and isoflurane. Core temperatures were ≈34°C by the end of surgery. The compensated core temperature at which visible shivering and a 20% decrease in steady-state oxygen consumption was recorded identified the shivering threshold. A blood sample for opioid concentration was obtained from each patient at this time. The ability of each opioid to reduce the shivering threshold was evaluated using linear regression.**

***Results:*** **End-tidal isoflurane concentrations were <0.2% in each group at the time of extubation, and shivering occurred ≈1 h later. Meperidine linearly decreased the shivering threshold: threshold (°C) = −2.8 · [meperidine (μg/ml)] + 36.2; $r^2$ = 0.64, *P* = 0.0005. Sufentanil also linearly decreased the shivering threshold: threshold (°C) = −7.8 · [sufentanil (ng/ml)] + 36.9; $r^2$ = 0.46, *P* = 0.02.**

***Conclusions:*** **At a given dose, sufentanil inhibited shivering 2,800 times better than meperidine. However, the equianalgesic ratio of these drugs is approximately 4,900. That is, meperidine inhibited shivering better than would be expected based on the equianalgesic potency ratio. These data are thus consistent with clinical observations suggesting that meperidine indeed possesses special antishivering activity. (Key words: Hypothermia; opioid; shivering; temperature; thermoregulation; vasoconstriction.)**

THE thermoregulatory effects of alfentanil[1] and meperidine[2] have been established in volunteers. Alfentanil reduces both the vasoconstriction and shivering thresholds (triggering core temperatures).[1] Meperidine, a combined μ- and κ-receptor agonist, apparently inhibits shivering better than equianalgesic concentrations of alfentanil.[2] This special action of meperidine may be mediated in part by activation of kappa opioid receptors.[3]

Volunteer studies have the advantage of allowing highly controlled experimental conditions. Further, it is generally possible to simultaneously evaluate the three major thermoregulatory defenses: sweating, vasoconstriction, and shivering. Nonetheless, considerable caution is appropriate when extrapolating shivering thresholds determined in volunteers to actual patients after surgery. First, some spontaneous postoperative tremor may not be normal shivering.[4,5] Second, control of even normal thermoregulatory shivering is modulated by many factors, including hypoxia, hypercarbia, and pain.[6–11] Respiratory difficulties are, of course, common in postoperative patients, as is pain.

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Many studies have evaluated potential treatments for postoperative shivering. Meperidine, for example, is generally reported to be more effective than pure $\mu$-receptor agonists.[12,13] Other investigators, however, report comparable efficacy.[14,15] Unfortunately, most studies of postoperative shivering are difficult to interpret because they fail to (1) compensate for kinetic differences among tested drugs, (2) maintain stable drug levels, (3) measure plasma concentrations, (4) evaluate the dose dependence of each drug, and (5) control for residual anesthetics.

A further difficulty is that previous studies define efficacy only by the treatment's ability to arrest shivering, rather than by determining concentration-dependent response thresholds. The problem with this approach is that the data are highly population specific, applying only to the observed core and skin temperatures and particular level of pain and adrenergic activation. The results of these studies thus are difficult to generalize. Finally, many studies include a wide range of ages, although shivering is significantly impaired[16] and relatively rare[17] in the elderly.

Our first task was to develop a method to determine postoperative shivering thresholds while maintaining the thermoregulatory and pharmacokinetic controls typical in volunteer studies. Our second goal was to quantify concentration-dependent reductions of the shivering threshold by meperidine and sufentanil in patients after operation. We chose sufentanil as the control opioid because its ability to inhibit shivering has not been determined.

## Methods

With approval from the Ethics Committee of the Hôpital Ambroise Paré and informed patient consent, we studied 30 patients classified as American Society of Anesthesiologists physical status 1 and 2. They were 18- to 40-yr-old and recovering from lower-limb orthopedic surgery that lasted at least 1 h. None was obese, febrile, taking $\beta$-receptor blockers, $\alpha_2$-receptor agonists, monoamine oxidase inhibitors, chlorpromazine, or tricyclic antidepressants. None had a history of thyroid or neuromuscular disease, dysautonomia, or Raynaud's syndrome. This study started in 1994, and data collection concluded in 1996; patient recruitment was thus finished before publication of the major studies showing adverse patient outcomes after mild perioperative hypothermia.[18]

*Protocol*

Patients were randomly assigned to receive meperidine or sufentanil and to three different target plasma concentrations of each. The target concentrations for meperidine were 0.15, 0.3, and 0.6 $\mu$g/ml; for sufentanil, the concentrations were 0.1, 0.15, and 0.2 ng/ml. These concentrations were chosen to span a range that would provide adequate pain relief while maintaining spontaneous postoperative ventilation.[19]

Opioids were administered in a double-blinded manner by infusions started $\approx$30 min before induction of anesthesia and continued throughout the first several hours of postanesthetic recovery. Specific infusion profiles were obtained by computer simulations using the SIPHAR (PHARM) program (SIMED, Inc., South Africa),[20] and were based on previously described sufentanil[21] and meperidine[22] pharmacokinetics, assuming linearity within the stipulated concentration intervals.

Anesthesia was induced, without premedication, by administration of 3–4 mg/kg propofol and 0.1 mg/kg vecuronium. The patients' tracheas were intubated, and ventilation was mechanically controlled to keep end-tidal carbon dioxide tension values at 30–35 mmHg. The fresh gas flow was maintained at 2 l/min *via* a semiclosed circle system without airway heating or humidification. Anesthesia was maintained with isoflurane in 60% nitrous oxide. Isoflurane was administered based on the clinical judgment of the attending anesthesiologist, with the general goal of maintaining mean arterial blood pressure within 20% of baseline values. No additional muscle relaxant was given. Patients were not actively warmed during anesthesia, and passive insulation was restricted to a single layer of surgical draping; intravenous fluids were not warmed.

When surgery was finished, isoflurane administration was discontinued. Residual neuromuscular block was not antagonized; however, supramaximal train-of-four stimulation of the ulnar nerve at the wrist confirmed complete recovery of muscular strength in all cases. Patients were transported to the postanesthetic care unit and then extubated. During recovery, patients were covered by a single blanket and were not actively warmed. Postoperative pain was treated, when necessary, by intravenous administration of proparacetamol (2 g).

*Measurements*

Ambient temperature was measured by a thermocouple positioned at the level of the patient, well away from any heat-producing equipment. Core temperature

was measured at the tympanic membrane. The aural probe was inserted until the patients felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected a gentle rubbing of the attached wire. The probe was then securely taped in place, the aural canal was occluded with cotton, and the external ear was covered with a gauze bandage.

Mean skin temperature was calculated from four sites using the formula $0.3 \cdot (T_{chest} + T_{deltoid}) + 0.2 \cdot (T_{thigh} + T_{calf})$.[23] Fingertip blood flow was evaluated using forearm − fingertip skin-surface temperature gradients.[24] Gradients exceeding 0°C were considered to indicate vasoconstriction. All temperatures were measured using Ellab thermometers and probes (Copenhagen, Denmark); they were recorded at 10-min intervals during surgery and every 5 min after operation.

Shivering was evaluated using oxygen consumption, as measured by a DeltaTrac metabolic monitor (Datex, Helsinki, Finland). Measurements began within 5 min of tracheal extubation. The system was used in canopy mode, and measurements were averaged over 1-min intervals and recorded every minute. (In this mode, 40 l/min is aspirated by the metabolic monitor from a plastic canopy surrounding the patient's head and upper chest). Both the absence of visible shivering and a 20% decrease in oxygen consumption, lasting at least 5 min, was considered a significant reduction in shivering intensity. The time at which shivering intensity decreased significantly was determined by an investigator blinded to the patients' core temperatures and drug and dose assignments.

Venous blood was sampled when patients arrived in the postanesthetic care unit and when a significant reduction in shivering intensity was identified. Samples were taken from the arm contralateral to the one in which opioids were being infused. Sufentanil plasma concentrations were determined using a radioimmunoassay slightly modified to improve the limits of quantification to 0.02 ng/ml.[25] An assay volume of 1 ml, previously adjusted to *p*H 10, was extracted on an Extrelut 3 column, with heptane-isoamyl alcohol (98.5:1.5) as the elution solvent. The solvent was evaporated to dryness, and the extract was dissolved in a small volume of distilled water containing 10% blank plasma. All or a fraction of this solution was evaluated by radioimmunoassay. Interassay precision and accuracy based on the measurement of quality-control samples were 10% and 108%, respectively. Meperidine plasma concentrations were determined using high-performance liquid chromatography.[26] Interassay precision and accuracy, based on the measurement of quality control samples, were 4% and 98%, respectively.

Heart rates were monitored continuously using three-lead electrocardiography. Blood pressures were determined at 5-min intervals during surgery and at 10-min intervals after operation. End-tidal carbon dioxide and isoflurane concentrations were quantified using an Cato gas analyzer (Dräger, Hamburg, Germany).

### *Data Analysis*

The cutaneous contribution to shivering is linear.[27] Thus we used measured skin and core temperatures, measured in degrees centigrade, to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature:

$$T_{core(calculated)} = T_{Core} + \left(\frac{\beta}{1 - \beta}\right)[T_{Skin} - T_{Skin(designated)}], \quad (1)$$

where the fractional contribution of the mean skin temperature to the threshold was termed $\beta$. $T_{Core(calculated)}$ thus equals the measured core temperature, $T_{Core}$, plus a small correction factor consisting of $\beta/(1 - \beta)$ multiplied by the difference between actual ($T_{skin}$) and designated [$T_{skin(designated)}$] skin temperatures. We previously described the derivation, validation, and limitations of this equation.[28] We used a $\beta$ factor of 0.2 for shivering.[27] The shivering threshold (at a designated mean skin temperature of 34°C) was calculated from measured core and mean skin temperatures when shivering intensity decreased significantly. The shivering threshold was thus the corrected core temperature when shivering stopped.

Demographic and morphometric characteristics of the volunteers and their anesthetic management, hemodynamic responses, and thermoregulatory responses were compared using unpaired, two-tailed *t* tests. Previous studies have shown that opioids linearly decrease the shivering threshold.[1,2] Consequently, the concentration dependence of the shivering threshold for meperidine and sufentanil was determined using linear regression. The ratio of the regression slopes indicated the relative efficacy of each opioid in blocking postoperative shivering.

**Table 1. Morphometric and Demographic Characteristics**

| | Meperidine | Sufentanil |
|---|---|---|
| Male/female | 10/5 | 10/5 |
| Age (yr) | 28 ± 7 | 28 ± 6 |
| Height (cm) | 173 ± 11 | 174 ± 8 |
| Weight (kg) | 74 ± 14 | 68 ± 10 |

Data are mean ± SD. There were no statistically significant differences between the patients given meperidine and sufentanil.

## Results

Morphometric and demographic characteristics of the patients given meperidine and sufentanil were similar (table 1). The duration of surgery, anesthetic management, and intraoperative hemodynamic responses also were similar in the two groups. Only 4 of 15 patients given meperidine and 3 of 15 given sufentanil required proparacetamol treatment for postoperative pain.

Core temperatures were typically near 34°C at the end of surgery. All patients shivered, and all were vasoconstricted (skin-temperature gradient >0°C) during shivering. Hemodynamic responses, expired gas concentrations, and mean skin temperatures were comparable at the shivering threshold in the patients given each opioid (table 2).

Individual plasma opioid concentrations were similar immediately after surgery and at the shivering threshold, differing by 0.01 ± 0.16 μg/ml in the patients given meperidine and by 0.01 ± 0.03 ng/ml in those given sufentanil. Individual plasma opioid concentrations at the shivering threshold were similar to the target concentrations, differing by 0.05 ± 0.08 μg/ml in the patients given meperidine and by 0.00 ± 0.02 ng/ml in those given sufentanil.

Meperidine linearly decreased the shivering threshold: Threshold (°C) = −2.8 · [meperidine (μg/ml)] + 36.2; $r^2$ = 0.64, $P$ = 0.0005. Sufentanil also linearly decreased the shivering threshold: Threshold (°C) = −7.8 · [sufentanil (ng/ml)] + 36.9; $r^2$ = 0.46, $P$ = 0.02. Sufentanil thus inhibited shivering approximately 2,800 times as well as meperidine did (fig. 1).

## Discussion

Both core and skin temperatures contribute to thermoregulatory control.[27,29] This is of little consequence for thermoregulatory investigations in animals because core temperature can be manipulated independently by implanted devices. The issue is somewhat more problematic in humans though because it is rarely practical to implant suitable heat exchangers. Nonetheless, various human models have been developed to determine the effects of drugs on thermoregulatory response thresholds. For example, core temperature can be reduced while skin temperature is maintained by water immersion,[30] skin temperature manipulations can be restricted to insensate limbs during regional anesthesia,[31] the core can be cooled in isolation by central-venous infusion of fluid,[32] or skin and core temperatures can be allowed to vary with subsequent arithmetic compensation for the changes in each.[28] Each of these models has been used with some success in volunteers.

The postoperative period, however, presents additional challenges for thermoregulatory investigations. Skin and core temperatures, for example, differ among patients and often change rapidly during the initial phase of recovery. In addition, most patients are given

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

| | Meperidine | Sufentanil |
|---|---|---|
| Preoperative core temperature (°C) | 36.6 ± 0.3 | 36.7 ± 0.2 |
| Duration of surgery (h) | 2.0 ± 0.9 | 2.0 ± 0.7 |
| Intraoperative end-tidal $P_{CO_2}$ (mmHg) | 34 ± 2 | 33 ± 3 |
| Intraoperative end-tidal [isoflurane] (%) | 0.9 ± 0.2 | 0.9 ± 0.2 |
| Intraoperative mean arterial blood pressure (mmHg) | 76 ± 8 | 76 ± 11 |
| Intraoperative heart rate (bpm) | 67 ± 11 | 63 ± 6 |
| Administered intraoperative fluid (L/h) | 0.6 ± 0.2 | 0.7 ± 0.3 |
| Final intraoperative core temperature (°C) | 34.3 ± 0.5 | 34.1 ± 0.5 |
| End-tidal [isoflurane] at extubation (%) | 0.18 ± 0.06 | 0.14 ± 0.06 |
| Postoperative ambient temperature (°C) | 20.8 ± 0.9 | 20.8 ± 0.8 |
| Time to shivering threshold (h) | 1.0 ± 0.3 | 1.0 ± 0.2 |
| Skin temperature gradient at threshold (°C) | 5.4 ± 1.0 | 5.8 ± 1.2 |
| Mean arterial blood pressure at threshold (mmHg) | 94 ± 8 | 102 ± 17 |
| Heart rate at threshold (bpm) | 70 ± 10 | 86 ± 24 |
| Mean skin temperature at threshold (°C) | 32.6 ± 1.1 | 33 ± 1.0 |

Threshold = cessation of shivering.

Data are means ± SD. Only heart rate at the shivering threshold differed significantly in the two treatment groups.

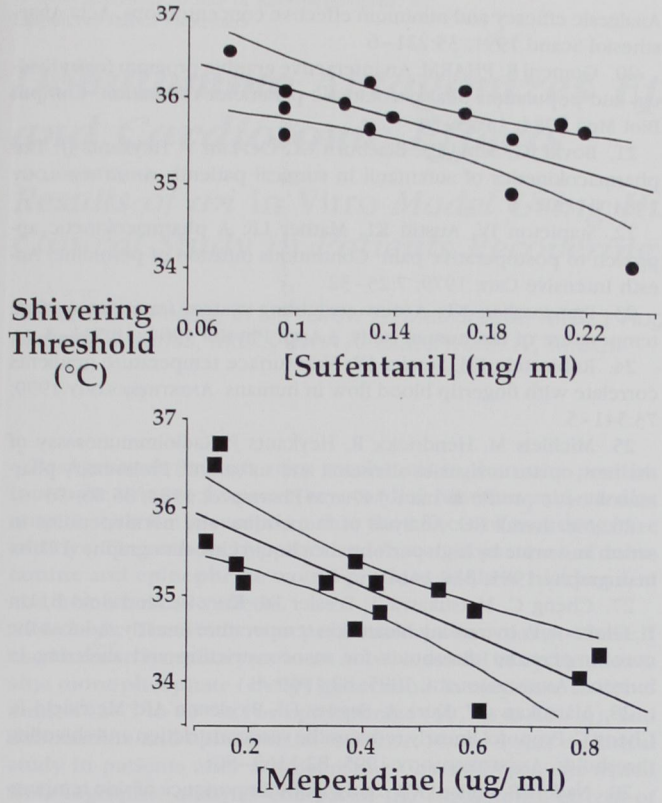


**Fig. 1. Meperidine linearly decreased the shivering threshold: Threshold (°C) = −2.8 · [meperidine (μg/ml)] + 36.2; $r^2$ = 0.64. Sufentanil also linearly decreased the shivering threshold: Threshold (°C) = −7.8 · [sufentanil (ng/ml)] + 36.9; $r^2$ = 0.46. Sufentanil thus inhibited shivering 2,800 times as well as meperidine did. The regression slopes are indicated by straight lines; the curved lines show the 95% CIs for the mean threshold.**

many drugs during operation, the concentrations of which typically decrease rapidly during recovery. These reductions in anesthetic concentrations are often further complicated by the postoperative treatment of surgical pain with opioids. Because anesthetics,[33] opioids,[1,2] and many anesthetic adjuvants[28,34] possess substantial thermoregulatory effects, it is often difficult to interpret observed postoperative thermoregulatory response patterns.

The method used in our investigation circumvents some of the design limitations common in previous studies. There are several important features. (1) We used only a single opioid in each patient and administered the drug by infusion to maintain steady-state plasma concentrations. Samples obtained at the shivering threshold were thus likely to reflect effect-site concentrations. (2) We applied arithmetic compensation for skin temperature alterations using the established relative contributions of skin and core temperatures to thermoregulatory control.[27] This compensation is necessary because higher drug doses are associated with lower thresholds and therefore lower skin temperatures. (3) Patients were not premedicated, and the only other intravenous drug likely to alter thermoregulatory responses (propofol) was restricted to anesthetic induction and must have been mostly metabolized by the time of recovery. Similarly, nitrous oxide surely dissipated rapidly after anesthesia. Some isoflurane inevitably remained during the postanesthetic period. End-tidal concentrations of anesthetic were already relatively low (<0.2%) at the time of tracheal extubation, and surely they were considerably lower at the shivering threshold ≈1 h after tracheal extubation.

The gain of shivering (incremental intensity increase with core cooling beyond the threshold) and its maximum intensity remain normal during meperidine and alfentanil administration.[35] Consequently, inhibition of shivering by opioids is mediated by a reduction in the shivering threshold. Both meperidine and sufentanil linearly inhibited shivering. Meperidine decreased the shivering threshold by about one half as much as previously reported in volunteers,[1] possibly because isoflurane *per se* facilitates shivering-like muscular activity.[4] It is also likely that surgical pain facilitates shivering in patients after operation.[10,11]

At a given dose, sufentanil inhibited shivering 2,800 times better than did meperidine. However, the equianalgesic ratio of these drugs is approximately 4,900.[36] That is, meperidine inhibited shivering better than would be expected based on the equianalgesic potency ratio. These data are thus consistent with clinical observations suggesting that meperidine possesses special antishivering activity.[12,13] They also are consistent with volunteer studies showing that meperidine inhibits shivering nearly twice as much as equianalgesic concentrations of alfentanil.[1,2] Available data thus suggest that meperidine is more effective than equianalgesic concentrations of pure μ-receptor agonists, and that its efficacy is mediated by a disproportionate reduction in the shivering threshold.

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