Dexmedetomidine and Meperidine Additively Reduce the Shivering Threshold in Humans

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Background and Purpose—Hypothermia might prove to be therapeutically beneficial in stroke victims; however, even mild hypothermia provokes vigorous shivering. Meperidine and dexmedetomidine each linearly reduce the shivering threshold (triggering core temperature) with minimal sedation. We tested the hypothesis that meperidine and dexmedetomidine synergistically reduce the shivering threshold without producing substantial sedation or respiratory depression.

Methods—We studied 10 healthy male volunteers (18 to 40 years) on 4 days: (1) control (no drug); (2) meperidine (target plasma level 0.3 µg/mL); (3) dexmedetomidine (target plasma level 0.4 ng/mL); and (4) meperidine plus dexmedetomidine (target plasma levels of 0.3 µg/mL and 0.4 ng/mL, respectively). Lactated Ringer’s solution (~4°C) was infused through a central venous catheter to decrease tympanic membrane temperature by ~2.5°C/h; mean skin temperature was maintained at 31°C. An increase in oxygen consumption >25% of baseline identified the shivering threshold. Sedation was evaluated by using the Observer’s Assessment of Sedation/Alertness scale. Two-way repeated-measures ANOVA was used to identify interactions between drugs. Data are presented as mean±SD; P<0.05 was statistically significant.

Results—The shivering thresholds on the study days were as follows: control, 36.7±0.3°C; dexmedetomidine, 36.0±0.5°C (P<0.001 from control); meperidine, 35.5±0.6°C (P<0.001); and meperidine plus dexmedetomidine, 34.7±0.6°C (P<0.001). Although meperidine and dexmedetomidine each reduced the shivering threshold, their interaction was not synergistic but additive (P=0.19). There was trivial sedation with either drug alone or in combination. Respiratory rate and end-tidal Pco2 were well preserved on all days.

Conclusions—Dexmedetomidine and meperidine additively reduce the shivering threshold; in the small doses tested, the combination produced only mild sedation and no respiratory toxicity. (Stroke. 2003;34:1218-1223.)

Key Words: body temperature regulation • dexmedetomidine • hypothermia • meperidine • stroke • temperature

Considerable animal data indicate that even mild hypothermia provides substantial protection against cerebral ischemic or hypoxic brain injury.1,2 In humans, hypothermia was reported to be an effective treatment for traumatic brain injury,3 although a subsequent study failed to confirm this observation.4 Mild hypothermia improves neurologic outcomes in survivors of out-of-hospital cardiac arrest.5,6 In acute stroke patients, body temperature is associated with initial stroke severity, infarct size, and mortality,7 and low body temperature on admission is an independent predictor of good short-term outcome.8 Hypothermia also appears to reduce intracranial pressure and might improve recovery from catastrophic strokes resulting from middle cerebral artery occlusion.9 Therapeutic mild to moderate hypothermia thus remains a promising treatment for ischemic brain injury.

In preliminary trials testing the feasibility and safety of therapeutic hypothermia in stroke patients,10,11 it proved difficult to induce mild or moderate hypothermia in unanesthetized patients10 because effective thermoregulatory defenses are maintained in most stroke victims.12 Induction of therapeutic hypothermia is thus complicated by the need to overcome arteriovenous shunt vasoconstriction and shivering and to do so without provoking extreme thermal discomfort or sympathetic nervous system activation—neither of which would be appropriate in these fragile patients. Drugs known to markedly impair thermoregulatory defenses are all anesthetics15 or major sedatives,16 which produce unacceptable amounts of respiratory depression for patients outside critical care settings. The search thus continues for a drug or drug combination that sufficiently impairs thermoregulatory de-
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fenses without simultaneously producing unacceptable toxicity.

Meperidine is probably the single most useful antishivering drug. It is effective for postoperative shivering and, unlike other drugs, decreases the shivering more than the vasoconstriction threshold. Meperidine is a complex drug that combines agonist effects at μ- and κ-opioid receptors, has local anesthetic activity, and has anticholinergic properties. Although μ-receptor agonists slightly and proportionately reduce the shivering and vasoconstriction thresholds, the drug’s anticholinergic and κ effects apparently do not explain meperidine’s special antishivering action. Unfortunately, plasma concentrations near 1.3 μg/mL are required to induce moderate hypothermia (ie, 33.5°C) with meperidine alone; at such concentrations, even young, healthy humans no longer reliably breathe spontaneously.

The α2-receptor agonists are another important class of antishivering drugs that, unlike meperidine, produce little respiratory toxicity. Intravenous dexmedetomidine reduces both the vasoconstriction and shivering thresholds. Interestingly, meperidine is an agonist at α2-adrenoceptors as is dexmedetomidine. This suggests that the combination of meperidine and dexmedetomidine might produce at least additive—and perhaps synergistic—antishivering activity. An additive or synergistic interaction would presumably augment the antishivering effect of meperidine, with little or no additional respiratory toxicity. We therefore tested the hypothesis that meperidine and dexmedetomidine synergistically reduce the shivering threshold.

Methods

With approval of the Human Studies Committee at the University of Louisville and informed consent, we studied 10 healthy male volunteers. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud’s syndrome.

Protocol

The volunteers fasted for 8 hours before each study day. They were minimally clothed and rested supine on a standard operating room table. Ambient temperature was maintained near 21°C. Each volunteer was studied on 4 days: (1) control, no drug; (2) dexmedetomidine at a target plasma concentration of 0.4 ng/mL; (3) meperidine at a target plasma concentration of 0.3 μg/mL; and (4) dexmedetomidine and meperidine combination at target concentrations of 0.4 ng/mL and 0.3 μg/mL, respectively. Each study day was separated by at least 48 hours.

Dexmedetomidine was delivered by a target-controlled infusion system starting 20 minutes before active cooling. The infusion pump (Harvard Apparatus 22, Harvard Apparatus) was controlled by STANPUMP software (version 4/98; http://anesthesia.stanford.edu/pkpd/). The meperidine infusion profile was based on the plasma drug-efflux techniques with coefficients estimated from published pharmacokinetic data.

A central catheter was introduced into the superior vena cava through an antecubital vein. This catheter was used for cold-fluid infusion and blood sampling. A venous catheter was inserted into the other arm for drug administration. Throughout the study period, mean skin temperature was maintained at 31°C by adjusting the temperature of circulating-water (Cincinnati Sub-Zero) and forced-air (Augustine Medical, Inc) warmers. Furthermore, the back, upper body, and lower body were individually maintained at the designated skin temperature.

Lactated Ringer’s solution cooled to ~4°C was infused at rates sufficient to decrease tympanic membrane temperature 1 to 2°C/h.

Fluid was given until the shivering threshold was identified or a total of 70 mL/kg was given.

Measurements

Heart rate was measured continuously with an electrocardiograph; blood pressure was determined oscillometrically at 5-minute intervals at the left ankle. A pulse oximeter continuously measured arterial oxygen saturation. All temperatures were recorded with thermocouples (Mon-a-Therm, Mallinckrodt Anesthesiology Products, Inc). Core temperature was recorded from the tympanic membrane. Volunteers inserted the aural probe until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when volunteers easily detected 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 determined from 15 area-weighted sites. Temperatures were recorded from thermocouples connected to calibrated 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Iso-Thermex, Columbus Instruments International Corp). Individual and mean skin temperatures were computed by a data acquisition system, displayed at 1-second intervals, and recorded at 1-minute intervals.

Arteriovenous shunt vasomotor tone was evaluated with forearm-minus-fingertip and calf-minus-toe skin temperature gradients. There is an excellent correlation between skin temperature gradients and volume plethysmography. Vasconstriction was defined by a forearm skin temperature gradient exceeding 0°C.

Oxygen consumption, as measured with a metabolic monitor (DeltaTrac, SensorMedics Corp) quantified shivering; the system was used in canopy mode. Measurements were averaged over 1-minute intervals and recorded every minute. End-tidal PCO2 was measured with a monitor (Ultima, Datex), and exhaust gases from this monitor were returned to the oxygen consumption monitor.

Blood for meperidine and dexmedetomidine concentrations was obtained just before the active cooling started and at the shivering threshold. A blank sample was obtained each day before drug administration. The samples were immediately centrifuged and frozen at −40°C until assayed.

For dexmedetomidine and meperidine, 1 mL plasma, 0.05 mL of 2 mg/L sufentanil (internal standard), 0.1 mL of 3 mol/L NaOH, and 6 mL of 2% pentanol in hexane were combined in a borosilicate glass tube, capped, and vortexed for 10 seconds. The samples were allowed to stand for 1 hour before centrifugation at 1000g for 10 minutes. The hexane phase was transferred to a second glass tube and evaporated to dryness under nitrogen at 40°C. The residue was reconstituted in 0.025 mL methanol, and the whole sample was injected into a gas chromatograph. The chromatograph used a programmable temperature vaporizer, a 30 m x 0.25 mm column (SGE Inc), and nitrogen-phosphorus detection. This method is linear to at least 1000 ng/mL for both drugs. For dexmedetomidine, the limit of quantification is 0.2 ng/mL, with a within-day coefficient of variation of 6.1% at 2 ng/mL. For meperidine, the limit of quantification is 5 ng/mL, with a within-day coefficient of variation of 5.0% at 50 ng/mL (n = 8).

Sedation was evaluated by using the responsiveness component of the Observer’s Assessment of Alertness/Sedation (OAA/S) score (Table 1). Behavioral responses (thermal comfort) were evaluated by using a 100-mm-long visual analog scale: 0 mm defined the worst imaginable cold, 50 mm defined thermal comfort, and 100 mm identified the worst imaginable heat. A new, unmarked scale was used for each test. On each study day, sedation score and thermal comfort were obtained 3 times: (1) before drug administration, (2) before active cooling started, and (3) at the shivering threshold.

Data Analysis

A sustained increase in oxygen consumption (VO2) of ≥25% identified the shivering threshold. The baseline for this analysis was the steady-state value (±5% variation in VO2) after drug infusion but before core cooling had started. On each study day, hemodynamic, respiratory, ambient temperature, and relative humidity data were averaged for each volunteer across the cooling period; these values

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were then averaged for all volunteers. Core and mean skin temperature data, as well as thermal comfort scores (visual analog scale) at the shivering threshold, were averaged across the volunteers for each study day. Sedation levels at the shivering threshold were presented as the number of subjects having 3 different OAA/S scores (5/4/3; see Table 1) on each study day. Results on the 4 study days were compared by Friedman’s repeated-measures ANOVA and Student-Newman-Keuls tests. Drug concentrations before core cooling were compared with those at the shivering threshold by using a paired t-test to confirm our steady-state assumption. The same test was used to compare drug concentrations between each drug day with the combination day.

The synergistic interaction between dexmedetomidine and meperidine was evaluated with the statistical methodology described by Slinker.33 The study was designed as a 2-factor experiment with 2 levels for each factor: the presence and absence of each of the 2 drugs. With this model, a statistically significant positive interaction term between the 2 drugs indicates that they act synergistically or antagonistically. A nonsignificant interaction term indicates that the drugs’ effects on the shivering threshold are additive. A repeated-measures ANOVA was used because each volunteer received all 4 treatments. Results are expressed as mean±SD; differences and the interaction term were considered statistically significant when P<0.05.

Results

The volunteers were 24±4 years old, weighed 75±11 kg, and were 178±8 cm tall. Ambient temperature, relative humidity, mean arterial pressure, heart rate, respiratory rate, average end-tidal PCO2, and SpO2 were similar on each study day. The mean skin temperature was maintained near 31°C. All of the volunteers were vasoconstricted before the cold-fluid infusion was started. On each of the 3 drug study days, plasma concentrations remained stable throughout the cooling period; in other words, concentrations at the beginning and end of the cooling period did not differ significantly. There were no differences in plasma concentrations between the drug and combination days for either dexmedetomidine or meperidine.

Sedation level at the shivering threshold, as defined by the OAA/S score, did not differ significantly on dexmedetomidine and meperidine days; the combination of dexmedetomidine and meperidine caused only mild sedation (Table 2).

Meperidine reduced the shivering threshold by 1.2°C— from 36.7±0.3°C on the control day to 35.5±0.6°C (P<0.001), and dexmedetomidine only reduced the shivering threshold by 0.7±0.5°C—to 36.0±0.5°C (P<0.001). The combination of meperidine and dexmedetomidine reduced the shivering threshold by 2.0±0.5°C—to 34.7±0.6°C (P<0.001; the Figure). There was no interaction between the 2 drugs in terms of effect on the shivering threshold (P=0.19). The combination of dexmedetomidine and meperidine thus additively reduced the shivering threshold.

Discussion

Dexmedetomidine22 and meperidine18 each as a function of dose linearly reduce the shivering threshold. Our results indicate that their combination further reduces the shivering threshold and that this interaction is additive. These data thus support supplementing meperidine with dexmedetomidine if the opioid alone is insufficient to block shivering.

TABLE 1. Responsiveness Component of the Observer’s Assessment of Alertness/Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is spoken loudly and/or repeatedly</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
</tr>
<tr>
<td>1</td>
<td>Does not respond to mild prodding or shaking</td>
</tr>
</tbody>
</table>

Data are presented as means±SDs or as the number of subjects at each of the three (5/4/3) score levels on the Observer’s Assessment of Alertness/Sedation (OAA/S) scale. Values in the upper section were first averaged over the infusion period and then averaged among the volunteers; values in the lower section are at the shivering threshold. VAS indicates visual analog scale.

Dexmedetomidine and meperidine levels did not differ significantly between the drug and combination days. *Statistically significant difference from control.

TABLE 2. Potential Confounding Factors and Important Results

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dexmedetomidine</th>
<th>Meperidine</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient temperature, °C</td>
<td>21.3±1.5</td>
<td>21.2±1.1</td>
<td>21.4±0.8</td>
<td>21.3±0.8</td>
</tr>
<tr>
<td>Relative humidity, %</td>
<td>29±6</td>
<td>29±8</td>
<td>29±9</td>
<td>30±7</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>102±2</td>
<td>101±2</td>
<td>97±11</td>
<td>99±11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±10</td>
<td>62±10</td>
<td>67±11</td>
<td>62±8</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>100±1</td>
<td>100±0</td>
<td>100±0</td>
<td>100±0</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>15±5</td>
<td>15±4</td>
<td>16±5</td>
<td>14±4</td>
</tr>
<tr>
<td>End-tidal PCO2, mm Hg</td>
<td>43±5</td>
<td>45±5</td>
<td>46±5</td>
<td>46±5</td>
</tr>
<tr>
<td>Dexmedetomidine, ng/mL</td>
<td>0.36±0.09</td>
<td>0.33±0.07</td>
<td>0.35±0.10</td>
<td></td>
</tr>
<tr>
<td>Meperidine, µg/mL</td>
<td></td>
<td>0.33±0.07</td>
<td>0.35±0.10</td>
<td></td>
</tr>
<tr>
<td>Total lactated Ringer’s, L</td>
<td>0.9±0.1</td>
<td>1.3±0.5*</td>
<td>1.5±0.5*</td>
<td>2.1±0.3*</td>
</tr>
<tr>
<td>Core cooling rate, °C/h</td>
<td>1.1±0.3</td>
<td>1.4±0.4</td>
<td>1.8±0.3*</td>
<td>1.9±0.5*</td>
</tr>
<tr>
<td>OAA/S score, 5/4/3</td>
<td>10/0/0</td>
<td>7/3/0</td>
<td>5/5/0</td>
<td>1/8/1*</td>
</tr>
<tr>
<td>Thermal comfort, VAS</td>
<td>22±13</td>
<td>20±11</td>
<td>26±12</td>
<td>27±9</td>
</tr>
<tr>
<td>Mean skin temperature, °C</td>
<td>31.0±0.1</td>
<td>31.0±0.0</td>
<td>30.9±0.1</td>
<td>30.9±0.1</td>
</tr>
<tr>
<td>Core temperature, °C</td>
<td>36.7±0.3</td>
<td>36.0±0.5*</td>
<td>35.5±0.6*</td>
<td>34.7±0.6*</td>
</tr>
</tbody>
</table>

Data are presented as means±SDs or as the number of subjects at each of the three (5/4/3) score levels on the Observer’s Assessment of Alertness/Sedation (OAA/S) scale. Values in the upper section were first averaged over the infusion period and then averaged among the volunteers; values in the lower section are at the shivering threshold. VAS indicates visual analog scale.

Dexmedetomidine and meperidine levels did not differ significantly between the drug and combination days. *Statistically significant difference from control.
Mechanisms of antishivering drugs

acting through independent mechanisms. Likely the result of the drugs' action at the threshold induced by meperidine and buspirone is that both dexmedetomidine and meperidine are central α2-activity,23 because both dexmedetomidine and meperidine are central α2-receptor agonists. The additive interaction between dexmedetomidine and meperidine contrasts with our previous observation that meperidine and buspirone interact synergistically.34 The synergistic reduction in the shivering threshold induced by meperidine and buspirone is likely the result of the drugs' action through independent mechanisms.

In previous studies,22,35 dexmedetomidine alone produced trivial sedative effect and no apparent ventilatory depression. Slightly more sedation was detected when the drug was combined with meperidine; however, our volunteers remained essentially alert and continued to breathe well throughout the study. The mixture of dexmedetomidine and meperidine thus joins meperidine and buspirone as a combination that provides substantial inhibition of shivering while causing only minimal sedation or ventilatory compromise. Minimal sedation and well-preserved ventilation are key because therapeutic hypothermia, to be practical, will need to be induced in patients who are monitored in a typical ward setting.

Although meperidine and buspirone interact synergistically, dexmedetomidine has greater antishivering activity than buspirone at clinically relevant concentrations.22,34 However, it is also considerably more sedating. The extent to which either combination inhibits shivering and the safety margins will thus depend on the specific doses used. Additional clinical experience will be required to determine which combination and doses provide optimal antishivering activity with minimal sedation and respiratory compromise.

There is currently little evidence that hypothermia protects against ischemia in humans, although the evidence is overwhelming in animals. There is certainly little basis for recommending a specific target temperature for therapeutic hypothermia. Nonetheless, target temperatures from 33°C to 34°C are being used clinically by some physicians and in ongoing clinical trials. The combination of meperidine and dexmedetomidine reduced the shivering threshold to 34.7°C, which some might consider insufficiently hypothermic. However, the observed shivering threshold of 34.7°C must be interpreted in light of 2 factors. The first is that we set mean skin temperature to 31°C, which is approximately 3°C less than typical for stroke patients in a ward or intensive care unit setting. We used this low skin temperature with the aim of raising the shivering threshold to minimize the risk from infusion of large amounts of cold fluid. Because skin temperature contributes 20% to control of vasoconstriction and shivering,36 each degree centigrade of cutaneous warming will compensate for approximately 0.2°C core hypothermia; the threshold at a more typical skin temperature would have been near 34°C. More aggressive cutaneous warming would further reduce the threshold. The second factor is that we used small doses of each drug to limit the amount of cold fluid we needed to administer to our volunteers and the hypothermia they experienced. The dexmedetomidine plasma concentrations could easily be doubled. Similarly, the meperidine concentration could be increased, especially in patients who are carefully monitored. Increasing either mean skin temperature or drug doses would further reduce the shivering threshold and bring it well within the range of temperatures that are commonly targeted. An additional factor to consider is that most stroke victims are elderly. Advanced age per se impairs thermoregulatory responses.37,38 It should thus be possible to induce comparable hypothermia in the elderly with even smaller drug doses or to induce greater hypothermia with similar drug doses.

Because mean-skin temperature was maintained near 31°C, our volunteers were already vasoconstricted before core cooling started. It was thus impossible to evaluate the vasoconstriction threshold. However, we have simultaneously determined the shivering and vasoconstriction thresholds in numerous previous studies.22 The shivering threshold has always been approximately 1°C less than the vasoconstriction threshold, except in the presence of meperidine, when there is a greater difference.18 It is therefore reasonable to assume that the vasoconstriction threshold in our volunteers would have been at least 1°C higher than the shivering threshold.

The vasoconstriction threshold is of considerable interest, because vasoconstriction is an effective thermoregulatory response. Vasoconstriction is the primary autonomic defense against cool environments and—once triggered—it prevents further hypothermia, even in anesthetized patients.39 It might thus be difficult to reduce core temperature below the vasoconstriction threshold with surface cooling. Internal cooling, such as we used, has no such limitation because heat is removed directly from the core thermal compartment. A further advantage of internal cooling is that patient comfort, which depends largely on skin temperature,40 can be improved by simultaneous cutaneous heating.

We induced core hypothermia by intravenous infusion of cold fluid. This method is unlikely to be suitable in stroke victims, especially if the target temperature is relatively low, because large volumes of fluid would be required. However,
it is an excellent model for a new generation of internal heat-exchanging catheters that induce core hypothermia without any net exchange of fluid.  Direct core cooling has distinct advantages when compared with conventional surface cooling: (1) It is much faster, because heat is removed directly from the core, rather than being required to pass through peripheral tissues, which insulate the core. (2) Less heat needs to be removed, and peripheral tissues stay relatively warm. Consequently, redistribution of heat from the periphery to the core or constraint of metabolic heat to the core has the potential to speed the return to normothermia during rewarming, if that is necessary. (3) Core cooling can be combined with simultaneous surface warming, which reduces the shivering threshold and improves thermal comfort. The rates of core cooling were restricted to a range of 1°C/h to 2°C/h, because we had previously shown that rates of that magnitude do not affect the shivering threshold and are unlikely to produce dynamic thermoregulatory responses.

We evaluated sedation with the well-accepted OAA/S scale that is designed to detect substantial variations in alertness and has been validated prospectively. Although it does not have the resolution to detect subtle degrees of sedation, it is unlikely that minimal amounts of sedation are clinically important in the context of therapeutic hypothermia for stroke and other life-threatening conditions. A more serious issue is ventilatory compromise that could limit administration of dexmedetomidine and meperidine in a typical ward setting. Respiratory rate and end-tidal PCO2 were well maintained with either drug and with the combination; however, we did not evaluate CO2 response curves or other measures of subtle ventilatory compromise.

In summary, dexmedetomidine and meperidine additively reduced the shivering threshold in healthy adults. The doses we tested decreased the threshold by \( \approx 2^\circ\text{C} \), with only minimal sedation or respiratory toxicity. This combination might thus facilitate studies evaluating the putative benefits of therapeutic hypothermia.

Acknowledgments

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References


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