Background: The analgesic nefopam does not compromise ventilation, is minimally sedating, and is effective as a treatment for postoperative shivering. The authors evaluated the effects of nefopam on the major thermoregulatory responses in humans: sweating, vasoconstriction, and shivering.

Methods: Nine volunteers were studied on three randomly assigned days: (1) control (saline), (2) nefopam at a target plasma concentration of 35 ng/ml (low dose), and (3) nefopam at a target concentration of 70 ng/ml (high dose, approximately 20 mg total). Each day, skin and core temperatures were increased to provoke sweating and then reduced to elicit peripheral vasoconstriction and shivering. The authors determined the thresholds (triggering core temperature at a designated skin temperature of 34°C) by mathematically compensating for changes in skin temperature using the established linear cutaneous contributions to control of each response.

Results: Nefopam did not significantly modify the slopes for sweating (0.0 ± 4.9°C · µg⁻¹ · ml; r² = 0.73 ± 0.32) or vasoconstriction (−3.6 ± 5.0°C · µg⁻¹ · ml; r² = −0.47 ± 0.41). In contrast, nefopam significantly reduced the slope of shivering (−16.8 ± 9.3°C · µg⁻¹ · ml; r² = 0.92 ± 0.06). Therefore, high-dose nefopam reduced the shivering threshold by 0.9 ± 0.4°C (P < 0.001) without any discernible effect on the sweating or vasoconstriction thresholds.

Conclusions: Most drugs with thermoregulatory actions—including anesthetics, sedatives, and opioids—reduction of the vasocostriction and shivering thresholds. However, nefopam reduced only the shivering threshold. This pattern has not previously been reported for a centrally acting drug. That pharmacologic modulations of vasoconstriction and shivering can be separated is of clinical and physiologic interest.

MAKING patients even a few degrees hypothermic provides more protection against tissue ischemia than available drugs. Hypothermia has been shown to improve neurologic outcomes after out-of-hospital cardiac arrest and is being tested for stroke and acute myocardial infarction. A difficulty with inducing hypothermia in humans is that even small reductions in core temperature trigger aggressive thermoregulatory defenses, including arteriovenous shunt vasoconstriction and shivering. Therefore, there is considerable interest in identifying drugs that defeat thermoregulatory defenses against hypothermia. Many drugs are known to induce thermoregulatory tolerance, but most are anesthetics or major sedatives. A potential alternative is nefopam, a non-sedative analgesic.

Nefopam is a benzoxazocine compound that is structurally related to orphenadrine and diphenhydramine. It is a centrally acting analgesic with both supraspinal and spinal sites of action. Nefopam is neither an opiate nor a nonsteroidal antiinflammatory drug. Nefopam does not induce respiratory depression, even postoperatively. It is available in Europe but is not approved by the Food and Drug Administration in the United States.

Clinical studies indicate that nefopam treats or prevents postoperative shivering for example, 0.15 mg/kg nefopam is as effective as 3 µg/kg clonidine in preventing postoperative shivering after orthopedic or abdominal surgery. 20 mg nefopam is as effective as 150 µg clonidine or 50 mg meperidine for prevention of shivering after hypothermic neurosurgery. However, patients given nefopam awaken sooner and experience less hypotension than those given clonidine.

Available data suggest that nefopam may inhibit thermoregulatory shivering without producing the sedative and hemodynamic effect of α₂ agonists or the respiratory consequences of opiates. Therefore, we evaluated the effects of nefopam on the three major thermoregulatory responses in humans: sweating, vasoconstriction, and shivering. Our specific hypothesis was that nefopam reduces the vasoconstriction and shivering thresholds.

Materials and Methods

With approval from the Ethics Committee of Hôpital Ambroise Paré (Boulogne, France) and informed consent, we studied nine healthy male volunteers. None of the volunteers were obese, were taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud syndrome.
Protocol

The volunteers had a light breakfast and refrained from caffeine for at least 8 h before the study. To avoid circadian fluctuations, studies were scheduled so that thermoregulatory responses were triggered at similar times on each of the 3 study days. During the studies, the volunteers rested in a supine position. They were minimally clothed, and ambient temperature was maintained between 20° and 22°C. The study was conducted in a double-blind, crossover fashion. The volunteers were studied on 3 randomly assigned days, each separated by at least 6 days: (1) control (saline), (2) nefopam at a target plasma concentration of 35 ng/ml (low dose), and (3) nefopam at a target concentration of 70 ng/ml (high dose).

An intravenous catheter was inserted into the right forearm for fluid and nefopam administration. Lactated Ringer’s solution was given as necessary to maintain mean arterial blood pressure greater than 60 mmHg. A 14-gauge catheter was inserted into a left antecubital vein and used for blood sampling.

Nefopam was given intravenously via a computer-controlled syringe pump. The infusion profile was based on published pharmacokinetic data. The time to peak plasma concentration was 20 min; the mean elimination half-life is approximately 240 min. This dosing scheme was intended to rapidly achieve therapeutic concentrations, minimize side effects during the initial phase, and maintain a therapeutic level throughout the study. The mean maximal target concentration (70 ng/ml) corresponded to a dose of 20 mg nefopam, which is a dose commonly used for postoperative analgesia.

Thermal manipulation began 30 min after the study drug was started. To minimize redistribution hypothermia, we prewarmed the volunteers for 30 min with a full-body forced-air warmer (Warm-touch; Mallinkrodt, Inc., St. Louis, MO) on low and a circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) set at 37°C. Active warming and cooling to avoid locally mediated vasoconstriction because this gradient corresponds to arterial warming and cooling to avoid locally mediated vasomotion. However, all other skin below the neck was similarly manipulated throughout each study day.

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

Measurements

Heart rate and pulse oximeter saturation were monitored continuously. Arterial pressure was determined oscillometrically at the ankle at 10-min intervals but also recorded at the sweating, vasoconstriction, and shivering thresholds. Oxygen consumption and carbon dioxide production were measured by a DeltaTrac metabolic monitor (Datex, Inc., Helsinki, Finland). The system was used in canopy mode with measurements averaged over 1-min intervals and recorded every minute.

Core temperature was measured at the tympanic membrane. The aural probe was inserted until the patient 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 (Tskin) was calculated from 10 sites, using the formula:

$$T_{skin}(°C) = 0.06 \cdot T_{forehead} + 0.09 \cdot T_{arm} + 0.06 \cdot T_{forearm}$$

$$+ 0.045 \cdot T_{hand} + 0.19 \cdot T_{back} + 0.095 \cdot T_{chest}$$

$$+ 0.095 \cdot T_{abdomen} + 0.19 \cdot T_{thigh} + 0.115 \cdot T_{calf}$$

$$+ 0.06 \cdot T_{foot}.$$  

All temperatures were measured using Ellab thermometers and probes (Ellab, Inc., Copenhagen, Denmark); they were electronically recorded at 10-s intervals until the end of the study.

A gauze compress was applied every 5 min on the forehead. As in previous studies, the appearance of moisture on the compress defined onset of sweating. This method correlates well with quantitative techniques. Fingertip blood flow was evaluated using forearm minus fingertip skin-surface temperature gradients. Gradients exceeding 0°C were indicative of vasoconstriction because this gradient corresponds to onset of the core temperature plateau. As in numerous previous studies, shivering was evaluated by a blinded observer and confirmed by a sustained increase in oxygen consumption to 30% greater than baseline.

Venous blood was sampled for nefopam concentrations when the volunteer reached the sweating, vasoconstriction, and shivering thresholds. Blood components were separated in a refrigerated centrifuge for 30 min, and the plasma samples were isolated and then stored at −20°C for subsequent analysis with high-performance liquid chromatography. Methanol (100 μl) was added to tubes containing 1-ml aliquots of plasma and the internal standard imipramine (1.5 mg/l, 0.1 ml). Solutions were alkalinized with a buffer solution (pH 12) and vortexed for 5 s. Cyclohexane (8 ml) was added, and the samples were agitated for 15 min and centrifuged for 10 min. The organic phase was transferred to a tube containing 0.3 ml HCl (0.1 N) and agitated and centri-
constriction and shivering is linear. Therefore, we used a mobile phase. The mobile phase was 300:700: acetonitrile/phosphate buffer, pH 6. Separation was accomplished at 4°C using a 150 × 4.6-mm, 5-μm C-18 column (Waters Associates, Milford, MA) with a flow rate of 1.2 ml/min. Ultraviolet absorbance was monitored at 210 nm. The response was linear to at least 100 ng/ml, with a detection limit of 1 ng/ml. The within-day coefficient of variation was 4.4% at 50 ng/ml, and the interday coefficient of variation was 2.4% at 50 ng/ml.

Thermal comfort was assessed at each threshold with a 100-mm visual analog scale, with 50 mm defined as thermal comfort, 0 mm as the most intense imaginable sensation of cold, and 100 mm as the most intense imaginable sensation of warm. Pain on nefopam injection, dizziness, headache, nausea, dry mouth, palpitation, and epigastric pain were recorded.

### Statistical Analysis

The cutaneous contribution to sweating and vasoconstriction and shivering linear. Therefore, we used linear regression models to calculate the core temperature threshold that would have been observed had the skin been maintained at a single designated temperature:

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

where the fractional contribution of mean skin temperature to the threshold was termed \( \beta \). Therefore, \( T_{\text{Core(calculated)}} \) equals the measured core temperature, \( T_{\text{Core}} \), plus a small correction factor consisting of \( \frac{\beta}{1 - \beta} \) multiplied by the difference between actual \( (T_{\text{Skin}}) \) and designated \( (T_{\text{Skin(designated)}}) \) skin temperatures. We have previously described the derivation, validation, and limitations of this equation. The coefficient of cutaneous contribution (\( \beta \)) was taken as 0.1 for sweating and 0.2 for vasoconstriction and shivering. The designated skin temperature was set at 34°C because that is a typical intraoperative value.

From the calculated core temperature thresholds on each study day, individual nefopam concentration-response curves for the sweating, vasoconstriction, and shivering thresholds were determined with linear regression. The average slopes and correlation coefficients \( (r^2) \) for the individual volunteers were then computed from these values. The average thresholds with each nefopam target dose were also computed.

Results at each target nefopam concentration were compared with repeated-measures analysis of variance and Bonferroni-Dunn tests for post hoc comparison. Side effect frequencies were compared using a chi-square test. Results are presented as mean ± SD or percent; \( P < 0.05 \) was considered statistically significant.

### Results

The volunteers were 30 ± 5 yr old, weighed 73 ± 15 kg, and were 177 ± 3 cm tall.

By design, plasma nefopam concentrations differed significantly on the low-dose (30 ng/ml) and the high-dose (60 ng/ml) days. On each study day, the plasma concentrations decreased with time, but the concentrations at the vasoconstriction and shivering thresholds were not significantly lower than at the sweating threshold.

The rate at which skin temperature changed varied from 2.9 to 4.3°C/h, but the rate at which core temperature changed was restricted to less than 2°C/h throughout the study.

Nefopam did not significantly modify the slope for sweating \( (0.0 ± 4.9 °C \cdot \mu g^{-1} \cdot ml; r^2 = 0.73 ± 0.32) \) or vasoconstriction \( (−3.6 ± 5.0 °C \cdot \mu g^{-1} \cdot ml; r^2 = 0.47 ± 0.41) \). In contrast, nefopam produced a significant concentration-dependent decrease in the shivering slope of \( 16.8 ± 9.3 °C \cdot \mu g^{-1} \cdot ml (r^2 = 0.89 ± 0.09; \text{fig. 1}) \) and in the shivering threshold of 0.9 ± 0.4°C (\( P ≤ 0.001 \); table 1). The average values for each threshold are shown in figure 2.

Nefopam administration did not significantly increase the sweating-to-vasoconstriction interthreshold range but did increase the vasoconstriction-to-shivering interthreshold range (table 1). Nefopam did not modify thermal sensation in volunteers. Heart rate after 30 min of saline was 72 ± 7 beats/min; after low-dose nefopam, it was 89 ± 15 beats/min and 89 ± 18 beats/min after high-dose nefopam. Therefore, both concentrations of nefopam significantly increased heart rate. Heart rates and mean arterial pressures were similar at each threshold on each of the study days (table 1).

Side effects experienced during nefopam administration are summarized in table 2. The volunteers were significantly more likely to become nauseated or to report pain on injection or a dry mouth during the study when nefopam rather than saline was infused. Profuse sweating during the initial 30 min of drug administration and high-dose nefopam administration. All side effects spontaneously resolved a few minutes after the end of the loading dose and did not recur during the steady state concentration infusion or the thermal manipulations. The volunteers fell asleep three times during loading of saline, seven times during low-dose nefopam, and five times during high-dose nefopam. All volunteers responded readily to their names, and none experienced speech impairment at any time during the study. None of the volunteers fell asleep during the thermal manipulations.
Discussion

Most drugs with thermoregulatory actions, including anesthetics, sedatives, and opioids synchronously reduce the vasoconstriction and shivering thresholds. In fact, the only distinct exception is meperidine, which reduces the shivering threshold twice as much as the vasoconstriction threshold—via unknown mechanisms. However, meperidine has distinct effects on vasoconstriction as well as shivering. In contrast, nefopam reduced the shivering threshold nearly 1°C without having any important effect on the vasoconstriction or sweating thresholds. This novel pattern has not previously been reported for any centrally acting drug. (Muscle relaxants, including dantrolene, impair shivering alone but do so peripherally.)

That vasoconstriction and shivering can be modulated independently is clinically important. With thermal manipulations mediated by surface heat exchange, for example, vasoconstriction slows heat transfer in unanesthetized subjects. Therefore, it is preferable in such circumstances to inhibit both vasoconstriction and shivering. Shivering similarly impairs thermal manipulations via internal heat-exchanging catheters. However, vasoconstriction may speed core temperature changes when heat is directly inserted or removed from the thermal core by decreasing the amount of heat that is dissipated into peripheral tissues. Furthermore, thermoregulatory vasodilation is associated with a reduction of approximately 20 mmHg in mean arterial pressure, which may be suboptimal in some patients (e.g., stroke victims). Therefore, it is likely that better understanding of thermoregulatory pharmacology will allow clinicians to optimize therapeutic temperature manipulations.

The thermoregulatory system is highly redundant, with afferent and efferent signals being integrated and modulated at numerous levels within the neuraxis. This complexity has impeded understanding of the molecular, cellular, and neurologic mechanisms that control normal body temperature, much less pharmacologic inhibition of normal thermoregulatory control. Therefore, it is of considerable physiologic interest to identify a drug that centrally impairs shivering without any apparent effect on vasoconstriction.

Mechanisms involved in the thermoregulatory effect of nefopam are not clearly established. However, in vitro and in vivo studies indicate that the analgesic properties of nefopam are related to its potent inhibition of serotonin (5-hydroxytryptamine), norepinephrine, and dopamine synaptosomal uptake. Monoamines are involved in the thermoregulatory pathways. The balance between modulator 5-hydroxytryptamine and norepinephrine inputs may be responsible for short-term thermoregulatory adaptive modifications of the heat-defense and cold-defense responses, with monoamines promoting hypothermia. Therefore, nefopam may promote hypothermia via a monoamine mechanism.

Other properties of nefopam may also contribute to its antishivering action. Nefopam may have a direct interaction with \( \alpha_2 \) adrenoceptors. Nefopam, like orphenadrine, is also a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. Magnesium sulfate and ketamine, which are competitive NMDA receptor antagonists, inhibit postanesthetic shivering. Therefore, inhibition of NMDA receptors may contribute to the antishivering effect of nefopam.

Numerous sites are involved in the control of the thermoregulatory shivering. Supraspinal sites are located in the hypothalamus, the pons, and the mesencepha-
Table 1. Major Results

<table>
<thead>
<tr>
<th></th>
<th>Saline (ng/mL)</th>
<th>Low-dose Nefopam (ng/mL)</th>
<th>High-dose Nefopam (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sweating threshold</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to sweating, h</td>
<td>0.8 ± 0.4</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76 ± 9</td>
<td>89 ± 11</td>
<td>89 ± 16</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>88 ± 10</td>
<td>94 ± 8</td>
<td>97 ± 10</td>
</tr>
<tr>
<td>Thermal sensation, mm</td>
<td>86 ± 9</td>
<td>81 ± 7</td>
<td>85 ± 6</td>
</tr>
<tr>
<td>Calculated threshold, °C</td>
<td>36.8 ± 0.2</td>
<td>36.8 ± 0.3</td>
<td>36.8 ± 0.3</td>
</tr>
<tr>
<td><strong>Vasoconstriction threshold</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to vasoconstriction, h</td>
<td>0.8 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>86 ± 10</td>
<td>94 ± 8</td>
<td>97 ± 10</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>89 ± 9</td>
<td>93 ± 7</td>
<td>98 ± 10</td>
</tr>
<tr>
<td>Thermal sensation, mm</td>
<td>40 ± 7</td>
<td>38 ± 7</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>Calculated threshold, °C</td>
<td>37.1 ± 0.3</td>
<td>37.1 ± 0.3</td>
<td>37.1 ± 0.3</td>
</tr>
<tr>
<td><strong>Shivering threshold</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to shivering, h</td>
<td>1.0 ± 0.3</td>
<td>2.0 ± 0.4*</td>
<td>2.2 ± 0.9†‡</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>68 ± 10‡</td>
<td>70 ± 11‡</td>
<td>68 ± 8‡</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>99 ± 7‡</td>
<td>98 ± 9</td>
<td>101 ± 14</td>
</tr>
<tr>
<td>Thermal sensation, mm</td>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>Calculated threshold, °C</td>
<td>36.7 ± 0.3</td>
<td>36.7 ± 0.4</td>
<td>36.7 ± 0.3</td>
</tr>
<tr>
<td><strong>Sweating-to-vasoconstriction interthreshold range, °C</strong></td>
<td>0.4 ± 0.4</td>
<td>0.6 ± 0.3</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td><strong>Vasoconstriction-to-shivering range, °C</strong></td>
<td>0.5 ± 0.2</td>
<td>0.8 ± 0.2*</td>
<td>1.2 ± 0.5†‡</td>
</tr>
</tbody>
</table>

Mean skin and core temperatures at sweating, vasoconstriction, and shivering and the thresholds calculated from these values at each target total plasma nefopam concentration. Hemodynamic responses and thermal comfort are also shown, along with the times required to reach each response. Thermal sensation was assessed using a 100-mm visual analog scale with 0 mm as neutral, 0 mm as the most intense sensation of cold, and 100 mm as the most intense sensation of warm. Data are presented as mean ± SD.

* Statistically significant difference vs. saline. † Statistically significant difference vs. small dose. ‡ Statistically significant difference vs. sweating.

In the rat, nefopam is a strong inhibitor of serotonin in the corpus striatum and of norepinephrine in the hypothalamus. Nefopam also has an effect in the pons that may partially explain its antishivering effect. Specific regional actions of nefopam may therefore explain its ability to impair shivering without similarly reducing the vasoconstriction threshold.

Alpha-2 agonists, such as clonidine and dexmedetomidine, have little or no effect on the sweating threshold, but both lower the vasoconstriction and shivering thresholds. These observations suggest that adrenoceptors are more involved in heat retention or production responses than in heat dissipation responses. Nefopam has a strong affinity for norepinephrine and serotonergic uptake sites, however, the serotonergic analgesic effect seems to be principally on descending pathways. Therefore, nefopam’s lack of effect on the sweating threshold might be explained by its central noradrenergic effects.

The spinal cord possesses thermoregulatory effectors that are normally under the inhibition of supraspinal centers. In rats, nefopam reduces the noxiously evoked spinal c-Fos protein expression and depresses the tail-flick test after intrathecal injection. In humans, nefopam decreases the Hoffman reflex in patients with back pain, indicating that nefopam affects human spinal motor neurons. However, it is difficult to even speculate to what extent spinal mechanisms contribute to the observed thermoregulatory effects of nefopam.

Tramadol is also a synaptic norepinephrine and serotonin uptake inhibitor. It slightly lowers the sweating thresholds at each nefopam concentration. Results are shown as mean ± SD.
tion and shivering thresholds. However, tramadol possesses an opioid effect and naloxone partially returned the thermoregulatory responses to control values. The different actions of tramadol and nefopam on autonomic thermoregulatory responses may thus be explained by the opioid properties of tramadol.

Based on previous experience with nefopam, we expected the side effects reported by our volunteers. All the adverse events disappeared spontaneously within 30 min even though the nefopam infusion continued. Therefore, it seemed that adverse events were due to rapid increases in cerebral concentration during loading rather than steady state concentrations per se. Both nefopam and tramadol administration are often associated with profuse sweating. However, sweating was transitory and unassociated with any reduction in the sweating threshold. Therefore, an additional possibility is that sweating in response to nefopam administration may result from direct simulation of eccrine glands rather than a thermoregulatory phenomenon.

In our unanesthetized volunteers, a typical postoperative analgesic blood nefopam concentration (70 ng/ml, which resulted from administration of approximately 20 mg) decreased the shivering threshold by roughly 1°C. In contrast, 0.12 mg/kg nefopam seemed to have a greater effect in patients recovering from neurosurgery. Only 2 of 20 patients shivered at a mean core temperature of 33.6°C. In any case, modest differences in plasma nefopam concentrations are of little consequence in this study because core temperature changes only slightly in the thermoregulatory model we used; furthermore, metabolism would presumably be increased at higher temperatures rather than the reverse. In any case, modest differences in plasma nefopam concentrations are of little consequence in this study because our primary analysis was based on individual concentration–response regressions.

In summary, nefopam administration had little effect on the sweating or vasoconstriction thresholds. However, the shivering threshold was reduced approximately 1°C by a plasma concentration of 55 ng/ml. This novel pattern has not previously been reported for any centrally acting drug. That pharmacologic modulations of vasoconstriction and shivering can be separated is of considerable clinical and physiologic interest.

### References


### Table 2. Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Saline, %</th>
<th>Low-dose Nefopam, %</th>
<th>High-dose Nefopam, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection</td>
<td>0</td>
<td>33*</td>
<td>56*</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11</td>
<td>44*</td>
<td>78*</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>44*</td>
<td>67*</td>
</tr>
<tr>
<td>Epigastria</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Data are presented as percent of total. *Statistically significant difference vs. saline.
NEFOPAM INHIBITS SHIVERING


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