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Nefopam, a Non-sedative Benzoxazocine Analgesic, Selectively Reduces the Shivering Threshold

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Abstract

Background—The analgesic nefopam does not compromise ventilation, is minimally sedating, and is effective as a treatment for postoperative shivering. We 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 (Small Dose), and 3) nefopam at a target concentration of 70 ng/ml (Large Dose, ≈ 20 mg total). Each day, skin and core temperatures were increased to provoke sweating and then reduced to elicit peripheral vasoconstriction and shivering. We 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 ($0.0 \pm 4.9^\circ\text{C}\cdot\mu\text{g}^{-1}\cdot\text{ml}$; $r^2 = 0.73 \pm 0.32$) or vasoconstriction ($-3.6 \pm 5.0^\circ\text{C}\cdot\mu\text{g}^{-1}\cdot\text{ml}$; $r^2 = -0.47 \pm 0.41$). In contrast, nefopam significantly reduced the slope of shivering ($-16.8 \pm 9.3^\circ\text{C}\cdot\mu\text{g}^{-1}\cdot\text{ml}$; $r^2 = 0.92 \pm 0.06$). Large-Dose nefopam thus reduced the shivering threshold by $0.9 \pm 0.4^\circ\text{C}$ ($P < 0.001$) without any discernable effect on the sweating or vasoconstriction thresholds.

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Summary Statement: Most drugs with thermoregulatory actions — including anesthetics, sedatives, and opioids — synchronously reduce the vasoconstriction and shivering thresholds. However, nefopam reduces the shivering threshold without affecting the sweating or vasoconstriction thresholds.

Conclusions—Most drugs with thermoregulatory actions — including anesthetics, sedatives, and opioids — synchronously reduce the vasoconstriction and shivering thresholds. Nefopam however reduced only the shivering threshold. This pattern has not previously been reported for a centrally acting drug. That pharmacologic modulation of vasoconstriction and shivering can be separated is of clinical and physiologic interest.

Keywords

Temperature; Thermoregulation; Nefopam; Shivering; Vasoconstriction; Threshold; Hypothermia

Introduction

Making patients even a few degrees hypothermic provides more protection against tissue ischemia than available drugs. Hypothermia has been shown to improve neurological outcomes after out-of-hospital cardiac arrest^{1,2} 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 arterio-venous shunt vasoconstriction and shivering.³ There is thus considerable interest in identifying drugs that defeat thermoregulatory defenses against hypothermia. Many drugs are known to induce thermoregulatory tolerance, but most are anesthetics^{4,5} or major sedatives.⁶ A potential alternative is nefopam, a non-sedative analgesic.

Nefopam is a benzoxazocine compound that is structurally related to orphenadrine and diphenhydramine.⁷ It is a centrally acting analgesic^{7,8} with both supra-spinal^{9,10} and spinal sites of action.^{11,12} Nefopam is neither an opiate nor a non-steroidal non-inflammatory drug.¹³ Nefopam does not induce respiratory depression, even in postoperative patients.¹⁴ 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.^{15–17} For example, nefopam, 0.15 mg/kg, is as effective as 3 µg/kg clonidine in preventing postoperative shivering after orthopedic or abdominal surgery.¹⁶ And 20 mg of nefopam is as effective as 150 µg clonidine or 50 mg meperidine for prevention of shivering after hypothermic neurosurgery.¹⁷ However, patients given nefopam awaken sooner and experience less hypotension than those given clonidine.

Available data thus suggest that nefopam may inhibit thermoregulatory shivering without producing the sedative and hemodynamic effect of α_2 agonists or the respiratory consequences of opiates. We therefore 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.

Methods

With approval from the Ethics Committee of Hôpital Ambroise Paré and informed consent, we studied nine healthy male volunteers. None was obese, taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's 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 three study days. During the studies, the volunteers rested supine. 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 three randomly assigned days, each separated by at least 6 days: 1) control (Saline), 2) nefopam at a target plasma concentration of 35 ng/mL (Small Dose), and 3) nefopam at a target concentration of 70 ng/mL (Large 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 > 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.¹⁸ The time to peak plasma concentration was 20 minutes; the mean elimination half-life is $\approx$ 240 minutes. 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) corresponds to a dose of 20 mg nefopam, which is a dose commonly used for postoperative analgesia.⁷

Thermal manipulation began 30 minutes after the study drug was started. To minimize redistribution hypothermia, we prewarmed the volunteers for 30 minutes with a full-body forced-air warmer (Warm-touch, Mallinckrodt, Inc., St. Louis, MO) on "low" and a circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) set at 37°C. Throughout the protocol, the arms were protected from active 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,⁵ 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 rewarmed all the way to the sweating threshold. The study ended each day when shivering was detected. Core temperature changes were restricted $\approx$ 2°C/h because this rate is unlikely to trigger dynamic thermoregulatory responses.³

Measurements

Heart rate and pulse oximeter saturation were monitored continuously. Arterial pressure was determined oscillometrically at the ankle at 10-minute 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., Finland).

The system was used in canopy-mode with measurements averaged over 1-minute intervals and recorded every minute.

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 occluded with cotton, and the external ear covered with a gauze bandage. Mean skin temperature (T_{Skin}) was calculated from ten sites, using the formula:

$$T_{\text{Skin}} (^{\circ}\text{C}) = 0.06 \cdot T_{\text{Forehead}} + 0.09 \cdot T_{\text{Arm}} + 0.06 \cdot T_{\text{Forearm}} + 0.045 \cdot T_{\text{Hand}} + 0.19 \cdot T_{\text{Back}} + 0.095 \cdot T_{\text{Chest}} + 0.095 \cdot T_{\text{Abdomen}} + 0.19 \cdot T_{\text{Thigh}} + 0.115 \cdot T_{\text{Calf}} + 0.06 \cdot T_{\text{Foot}}$$

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

A gauze compress was applied each 5 minutes on the forehead. As in previous studies,¹⁹ the appearance of moisture on the compress defined onset of sweating. This method correlates well with quantitative techniques.²⁰ Fingertip blood flow was evaluated using forearm minus fingertip, skin-surface temperature gradients.²¹ Gradients exceeding 0°C were indicative of vasoconstriction because this gradient corresponds to onset of the core-temperature plateau.²² As in numerous previous studies, shivering was evaluated by a blinded observer and confirmed by a sustained increase in oxygen consumption to 30% above 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 minutes, 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 imipramin (1.5 mg/L, 0.1 ml). Solutions were alkalized with a buffer solution (pH 12) and vortexed for 5 seconds. Cyclohexane (8 ml) was added and the samples were agitated for 15 minutes and centrifuged for 10 minutes. The organic phase was transferred to a tube containing 0.3 ml HCl (0.1 N) and agitated and centrifuged again. The organic phase was discarded and 200 μl of the aqueous phase was transferred and evaporated to dryness under nitrogen at 45°C . Samples were reconstituted in 0.2 ml mobile phase. The mobile phase was 300:700: acetonitrile/phosphate buffer, pH 6. Separation was accomplished at 4°C using a 150-mm by 4.6-mm, 5 μm C-18 column (Waters Associates, Milford, MA) with a flow rate of 1.2 ml/minute. UV 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 inter-day 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 upon nefopam injection, dizziness, headache, nausea, dry mouth, palpitation, and epigastric pain were recorded.

Statistical Analysis

The cutaneous contribution to sweating²³ and to vasoconstriction and shivering²⁴ is linear. We thus used measured skin and core temperatures in degrees centigrade at each threshold to calculate the core-temperature threshold that would have been observed had skin been maintained at a single designated temperature:

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

where the fractional contribution of mean skin temperature to the threshold was termed β . $T_{\text{Core(calculated)}}$ 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 [$T_{\text{skin(designated)}}$] skin temperatures. We have previously described the derivation, validation, and limitations of this equation.⁴ The coefficient of cutaneous contribution (β) was taken as 0.1 for sweating²³ and 0.2 for vasoconstriction and shivering.²⁴ 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 ANOVA and a Bonferroni-Dunn test for post hoc comparison. Side effect frequencies were compared using a χ^2 test. Results are presented as means $\pm$ SDs or percent; $P < 0.05$ was considered statistically significant.

Results

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

By design, plasma nefopam concentrations differed significantly on the small-dose (30 ng/ml) and the large-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 ($0.0 \pm 4.9^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$, $r^2 = 0.73 \pm 0.32$) or vasoconstriction ($-3.6 \pm 5.0^\circ\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$; $r^2 = 0.47 \pm 0.41$). In contrast, nefopam produced a significant concentration-dependent decrease in the shivering slope of $16.8 \pm$

$9.3^{\circ}\text{C}\cdot\mu\text{g}^{-1}\cdot\text{ml}$, $r^2 = 0.89 \pm 0.09$ (Fig. 1) and in the shivering threshold of $0.9 \pm 0.4^{\circ}\text{C}$ ($P = 0.001$, Table 1). The average values for each threshold are shown in Fig. 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 minutes of saline was 72 ± 7 beats per min (bpm); after small-dose nefopam, it was 89 ± 15 bpm and 89 ± 18 bpm after large-dose nefopam. Both concentrations of nefopam thus 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 complain about having pain upon injection or a dry mouth during the study when nefopam rather than saline was infused. Profuse sweating during the initial 30 minutes of drug administration (and not associated with cutaneous warming) was observed in two volunteers during low- and high-dose nefopam administration. All side effects spontaneously disappeared a few minutes after the end of the loading dose and did not reappear during the steady-state concentration infusion or the thermal manipulations. The volunteers fell asleep three times during loading of saline, seven times during the small-dose nefopam, and five times during large-dose nefopam. All volunteers responded readily to their names, and none suffered 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,^{4,5} sedatives,^{25,26} and opioids²⁷ — 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 threshold²⁸ — *via* unknown mechanisms.²⁹ However, meperidine has distinct effects on vasoconstriction as well as shivering. Nefopam, in contrast, reduced the shivering threshold nearly 1°C without having any important effect on the vasoconstriction or sweating thresholds. This is a novel pattern that 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.^{30,31} It is thus 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 an approximately 20 mmHg reduction in mean-arterial pressure which may be sub-optimal in some patients (*e.g.*, stroke victims).³² It is thus 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. It is thus of considerable physiological 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 nefopam's analgesic properties are related to its potent inhibition of serotonin (5-HT), norepinephrine, and dopamine synaptosomal uptake.^{10,12,33–35} Monoamines are involved in the thermoregulatory pathways.^{36,37} The balance between modulator 5-HT and norepinephrine inputs may be responsible for short-term thermoregulatory adaptive modifications of the heat-defense and cold-defense responses, with monoamines promoting hypothermia.^{4,5} Nefopam may therefore promote hypothermia via a monoamine mechanism.

Other properties of nefopam may also contribute to its anti-shivering action. Nefopam may have a direct interaction with α_2 -adrenoceptors.¹² Nefopam, like orphenadrine, is also a non-competitive NMDA receptor antagonist.³⁹ Magnesium sulfate and ketamine, which are competitive NMDA receptor antagonists, inhibit postanesthetic shivering.^{40,41} Inhibition of NMDA receptors may thus contribute to the anti-shivering 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 mesencephalon.³⁸ In the rat, nefopam is a strong inhibitor of serotonin in the corpus striatum and of norepinephrine in the hypothalamus.⁴² Nefopam also has an effect in the pons that may partially explain its anti-shivering effect.^{34,35,42} Specific regional actions of nefopam may thus explain its ability to impair shivering without similarly reducing the vasoconstriction threshold.

Alpha-2 agonists, such as clonidine and dexmedetomidine, have little⁴³ or no effect^{25,44} on the sweating threshold, but both lower the vasoconstriction and shivering thresholds.^{25,44,45} 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;^{34,35} however, the serotonergic analgesic effect seems to be principally on descending pathways.⁴⁶ Nefopam's lack of effect on the sweating threshold, therefore, might be explained by its central noradrenergic effects.

The spinal cord possesses thermoregulatory effectors that are normally under the inhibition of supra-spinal centers.⁴⁷ In rats, nefopam reduces the noxiously evoked spinal c-Fos protein expression¹¹ and depresses the tail-flick test after intrathecal injection.⁴⁸ In humans, nefopam decreases the Hoffman reflex in patients suffering from back pain,⁴⁹ indicating that nefopam affects human spinal motor neurons. However, it is hard 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.⁵⁰ It slightly lowers the sweating threshold and synchronously decreases the vasoconstriction and shivering thresholds.⁵¹ However, tramadol possesses an opiate effect and naloxone partially returned the thermoregulatory responses to control values.⁵¹ 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,⁵² the side effects reported by our volunteers were expected. All the adverse events disappeared spontaneously within 30 minutes even though the nefopam infusion continued. It thus appeared 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.^{7,50} However, sweating was transitory and unassociated with any reduction in the sweating threshold. An additional possibility is thus that sweating in response to nefopam administration may result from direct stimulation of eccrine glands rather a thermoregulatory phenomenon.

In our unanesthetized volunteers, a typical postoperative analgesic blood nefopam concentration (70 ng/ml that resulted from administration of ≈ 20 mg) decreased the shivering threshold by roughly 1°C. In contrast, 0.12 mg/kg of nefopam appeared to have a greater effect in patients recovering from neurosurgery.⁵³ Indeed, only 2 of 20 patients shivered at a mean core temperature of 33.6°C. However, there were numerous factors that presumably contributed to thermoregulatory inhibition in these patients including residual anesthesia and opioids, cutaneous warming to 36.5°C, and neurosurgery *per se*.

An approximately 1°C reduction in the shivering threshold is itself unlikely to be sufficient for induction of therapeutic hypothermia in unanesthetized patients. However, nefopam does not impair ventilation and its other side effects are minimal and of short duration. It is thus likely that nefopam can be combined with other drugs to produce substantial thermoregulatory tolerance with minimal side effects. This strategy has been used, for example, with meperidine and buspirone which synergistically reduce the shivering threshold.⁵⁴

Plasma nefopam concentrations were slightly greater during sweating than at the vasoconstriction or shivering thresholds. Greater concentrations at sweating presumably result from an imperfection in our computer-controlled infusion profile since 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 since 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 $\approx 1^\circ\text{C}$ by a plasma concentration of 55 ng/ml. This is a novel pattern that has not previously been reported for any centrally

acting drug. That pharmacologic modulation of vasoconstriction and shivering can be separated is of considerable clinical and physiologic interest.

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Fig. 1.

The individual effects of increasing plasma nefopam concentration on the core temperatures triggering sweating (open circles and thin line), vasoconstriction (filled circles and medium line), and shivering (open triangles and thick line) in nine volunteers. Nefopam did not significantly change the sweating or vasoconstriction thresholds; however, the slope of shivering decreased significantly by $16.7 \pm 9.5^{\circ}\text{C} \cdot \mu\text{g}^{-1} \cdot \text{ml}$ and the shivering threshold by $0.9 \pm 0.4^{\circ}\text{C}$. All the thresholds (at a designated skin temperature of 34°C) were calculated from measured skin and core temperatures.

Fig. 2.

The average sweating, vasoconstriction, and shivering thresholds at each nefopam concentration. Results are shown as means $\pm$ SDs.

Table 1

Major Results.

		Saline	Small Dose Nefopam	Large Dose Nefopam
Sweating Threshold	Time to Sweating (h)	0.8 ± 0.4	0.8 ± 0.2	0.7 ± 0.2
	Heart Rate (beats per min)	76 ± 9	89 ± 11	89 ± 16
	Mean Arterial Pressure (mmHg)	86 ± 10	94 ± 8	97 ± 10
	Thermal Sensation (mm)	86 ± 9	81 ± 7	85 ± 6
	[Nefopam] (ng/ml)	-	32 ± 6	70 ± 6
	Mean Skin Temp (°C)	36.3 ± 0.4	36.2 ± 0.3	36.1 ± 0.6
	Core Temp (°C)	36.8 ± 0.2	36.9 ± 0.3	36.9 ± 0.3
	Calculated Threshold (°C)	37.1 ± 0.3	37.1 ± 0.3	37.1 ± 0.3
Vasoconstriction Threshold	Time to Vasoconstriction (h)	0.8 ± 0.4	1.2 ± 0.4	1.4 ± 0.9
	Heart Rate (beats per min)	86 ± 10	94 ± 8	97 ± 10
	Mean Arterial Pressure (mmHg)	89 ± 9	93 ± 7	98 ± 10
	Thermal Sensation (mm)	40 ± 7	38 ± 7	33 ± 10
	[Nefopam] (ng/ml)	-	27 ± 2	56 ± 13
	Mean Skin Temp (°C)	33.5 ± 1.2	33.2 ± 1.0	32.9 ± 1.0
	Core Temp (°C)	36.8 ± 0.2	36.7 ± 0.3	36.7 ± 0.3
	Calculated Threshold (°C)	36.7 ± 0.3	36.5 ± 0.4	36.5 ± 0.5
Shivering Threshold	Time to Shivering (h)	1.0 ± 0.3	2.0 ± 0.4*§	2.2 ± 0.9*†§
	Heart Rate (beats per min)	68 ± 10§	70 ± 11§	68 ± 8§
	Mean Arterial Pressure (mmHg)	99 ± 7§	98 ± 9	101 ± 14
	Thermal Sensation (mm)	12 ± 5	12 ± 5	9 ± 6
	[Nefopam] (ng/ml)	-	28 ± 4	55 ± 11
	Mean Skin Temp (°C)	31.0 ± 1.2	30.6 ± 1.1	29.2 ± 1.6*
	Core Temp (°C)	36.9 ± 0.2	36.6 ± 0.2	36.5 ± 0.3*
	Calculated Threshold (°C)	36.2 ± 0.2	35.8 ± 0.4*	35.3 ± 0.4*†
Sweating-to-Vasoconstriction Interthreshold Range (°C)		0.4 ± 0.4	0.6 ± 0.3	0.6 ± 0.3
Vasoconstriction-to-Shivering Range (°C)		0.5 ± 0.2	0.8 ± 0.2*	1.2 ± 0.5*†

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 50 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 means ± SDs

* Statistically significant difference *versus* Saline

† Statistically significant difference *versus* Small Dose.

§ Statistically significant difference *versus* Sweating.

Table 2

Side Effects.

	Saline	Small Dose	Large Dose
Pain at Injection (%)	0 %	33 % *	56 % *
Dry Mouth (%)	11%	44 % *	78 % *
Nausea (%)	0 %	44 % *	67 % *
Epigastria (%)	0 %	11 %	11 %
Palpitation (%)	0 %	22 %	11 %
Headache (%)	0 %	11 %	0 %
Dizziness (%)	0 %	11 %	22 %

Data are presented as percent of total.

* Statistically significant difference *versus* Saline.