Premedication with Famotidine Augments Core Hypothermia during General Anesthesia

Munetaka Hirose, M.D.,* Yumi Hara, M.D.,† Masahiko Matusaki, M.D.‡

Background: Animal studies have provided considerable evidence to support a role of histamine in the central nervous system in thermoregulation, and premedication with a histamine H₂ receptor antagonist before general anesthesia is used to reduce the risk of acid aspiration. The authors investigated whether premedication with famotidine had an effect on thermoregulation during general anesthesia.

Methods: In a randomized, placebo-controlled study, 30 ASA physical status 1 or 2 patients, scheduled for open abdominal surgery, were given either placebo or 40 mg oral famotidine 3 h before induction of anesthesia. Epidural buprenorphine (4 µg/kg) was injected, and anesthesia was maintained with 0.4–0.6% isoflurane and 66% nitrous oxide in oxygen. The tympanic membrane temperature was measured to assess core temperature, and forearm–fingertip and calf–toe skin-surface temperature gradients were used to assess peripheral vasconstriction. Tympanic membrane temperature triggering initial vasoconstriction (a skin temperature gradient of 0°C) identified the vasoconstriction threshold.

Results: Tympanic membrane temperature during surgery in the patients premedicated with famotidine was significantly less than those in the patients without famotidine. Famotidine significantly reduced the thermoregulatory threshold for vasoconstriction in the leg (35.0 ± 0.5°C, P < 0.05), compared to that in the placebo group (36.4 ± 0.6°C). Once triggered, thermoregulatory vasoconstriction produced a core-temperature plateau and no further hyperthermia was observed for the duration of the study. Neither mean arterial pressure nor heart rate were significantly different between the two groups.

Conclusions: Premedication with famotidine augments intraoperative hypothermia. The mechanism appears to be inhibition of centrally mediated thermoregulatory control. (Key words: Histamine, antagonists: famotidine. Temperature: regulation. Thermoregulation: vasoconstriction.)

* Staff Anesthesiologist, Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan.
† Fellow, Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan.
‡ Resident, Department of Anesthesia, Maizuru National Hospital, Kyoto, Japan.

Received from the Department of Anesthesia, Maizuru National Hospital, Maizuru, Kyoto, Japan. Submitted for publication April 20, 1995. Accepted for publication August 29, 1995.

Address reprint requests to Dr. Hirose: Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kamigyoku, Kyoto 602, Japan.

Anesthesiology, V 83, No 6, Dec 1995
histamine release, but a combination of H1- and H2-antagonists does.16,21 Cimetidine by itself is reported to decrease arterial pressure secondary to peripheral vasodilation in contrast to ranitidine and famotidine, which have no hemodynamic effect.22,23 To avoid the effect of vasodilation on thermoregulation, we therefore selected famotidine to investigate the central thermoregulatory effects of premedication with H2-antagonists.

Materials and Methods

Patients
A total of 30 patients (ASA Physical Status 1 or 2), aged 22–60 years scheduled for open abdominal surgery were enrolled in this study. None of them had any cardiopulmonary or autonomic disorders, or was taking any medications that affect cardiovascular function. The patients were randomly allocated to either of the two groups: orally administered placebo (control group, n = 15) or famotidine (famotidine group, n = 15). The study was approved by the Ethics Committee of our institution, and all patients gave their written informed consent before participating in the study.

Experimental Protocol
The patients received either the placebo or famotidine (40 mg) 3 h before induction of anesthesia. After transfer of the patient into the operating room, an intravenous catheter was inserted for administration of fluid (8 ml·kg\(^{-1} \cdot \text{h}^{-1}\) lactated Ringer’s solution). In all patients, an epidural catheter was placed via the T12-L1 or the L1-L2 vertebral interspaces while the patient was in the lateral position. A 3-ml test dose of 1% lidocaine with epinephrine (5 µg/ml) was then administered. Before induction of anesthesia, each patient received epidural 4 µg/kg buprenorphine in 5 ml saline. Anesthesia was induced with 5 mg/kg thiopental and was maintained with 0.4–0.6% isoflurane and 66% nitrous oxide in oxygen.

Vecuronium bromide (0.1 mg/kg) was used to facilitate tracheal intubation and also for muscle relaxation during surgery. All patients remained in the horizontal position during surgery. The ambient temperature in the operating room was maintained between 24 and 25°C whenever possible, but the patients were not actively warmed during the study. We did not use local epidural anesthetics during the study. Postoperative epidural analgesia was instituted with continuous infusion at 0.7 ml/h 0.25% bupivacaine containing buprenorphine (12 µg/ml) using a disposable balloon-operated infuser (Sure-fuser SFA-0503D, Nipro, Japan) for 3 days.

Indirect blood pressure (Pulsemate BX-5, Colin, Japan), heart rate, oxygen saturation, end-tidal carbon dioxide tension, and end-tidal isoflurane concentration (5250 RGM, Ohmeda, Louisville, CO) were monitored. Normocapnia (35–40 mmHg) was maintained during surgery. Blood loss was evaluated by weighing the surgical sponges and by measuring the blood volume in the suction containers. Blood lost was replaced with three times the volume of additional lactated Ringer’s solution.

Measurements
Skin temperature probes (PD-K161, Terumo, Japan) were attached onto the radial aspect of the forearm halfway between the elbow and the wrist, at the anterior mid-calf, and on opposite sites of the nail bed on the index finger and the big toe. Core temperature was measured using an infrared tympanic membrane thermometer (Quick-Thermo MC-500, Omron, Japan). We averaged the tympanic membrane temperature measured three times to reduce error. Peripherial vasoconstriction was quantified using skin-surface temperature gradients24,26: the upper extremity temperature gradients were monitored using the forearm minus finger skin-surface temperature gradients, and the lower extremity gradients using the calf minus toe skin-surface temperature gradients. The vasoconstriction thresholds was defined as the tympanic membrane temperature at which the gradient equaled zero and 4°C.

The tympanic membrane temperature, skin-surface temperature gradients, ambient temperature, end-tidal isoflurane concentration, mean arterial pressure, and heart rate were recorded before induction and every 15 min after skin incision until the end of the operation.

Statistics
The Kruskal-Wallis test for unpaired data was used to compare patient demographic data or thermoregulatory thresholds in the two groups. Between-group evaluation of each variable was conducted using one-way analysis of variance. Thereafter, Fisher’s least significant difference test was used to identify significant differences in various pairs of comparisons. The null hypothesis was rejected when \( P < 0.05 \). All values are reported as means ± SD.
FAMOTIDINE AND TEMPERATURE

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Famotidine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>5/10</td>
<td>5/10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51 ± 12</td>
<td>46 ± 16</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53 ± 7</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 ± 8</td>
<td>160 ± 9</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>181 ± 71</td>
<td>168 ± 54</td>
</tr>
<tr>
<td>Blood loss as of 60 min (g)</td>
<td>142 ± 141</td>
<td>199 ± 130</td>
</tr>
<tr>
<td>Fluid replacement as of 60 min (ml)</td>
<td>1,058 ± 343</td>
<td>1,101 ± 236</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Results

There were no significant differences between the two groups in age, body weight, height, or duration of surgery. The blood loss and fluid replacement volumes as of 60 min after the skin incision also did not differ significantly in the two groups (table 1). The two groups did not differ significantly in end-tidal isoflurane concentration or ambient operating room temperature (table 2). We confirmed that no patient complained about awareness during the surgery.

The tympanic membrane temperature in the famotidine group was significantly less than that in the control group during the surgery (fig. 1). Table 3 shows the vasoconstriction threshold and the number of patients whose forearm–fingertip and calf–toe temperature gradients equaled zero and 4°C. Vasoconstriction thresholds (the gradient = 0°C) with famotidine were 35.2 ± 0.9°C for the forearm–fingertip gradient and 35.6 ± 0.5°C for the calf–toe gradient, which were significantly less than those without famotidine of 36.2 ± 0.7 and 36.4 ± 0.6°C, respectively (P < 0.05). Mean arterial pressure and heart rate were virtually identical in the two groups.

Discussion

Premedication with famotidine augmented core hypothermia and reduced vasoconstriction threshold during open abdominal surgery under isoflurane anesthesia. The two groups with and without famotidine premedication did not differ in mean arterial pressure or heart rate. Famotidine is likely to decrease core tem-

Table 2. End-tidal Isoflurane Concentration and Ambient Operating Room Temperature

<table>
<thead>
<tr>
<th></th>
<th>Before Induction</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>75 min</th>
<th>End Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal isoflurane concentration (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
<td>0.52 ± 0.16</td>
<td>0.54 ± 0.42</td>
<td>0.55 ± 0.14</td>
<td>0.51 ± 0.29</td>
<td>0.52 ± 0.29</td>
<td>0.52 ± 0.30</td>
</tr>
<tr>
<td>Famotidine</td>
<td>—</td>
<td>0.52 ± 0.24</td>
<td>0.55 ± 0.35</td>
<td>0.57 ± 0.32</td>
<td>0.54 ± 0.32</td>
<td>0.54 ± 0.32</td>
<td>0.55 ± 0.32</td>
</tr>
<tr>
<td>Ambient operating room temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>24.6 ± 1.5</td>
<td>24.6 ± 1.0</td>
<td>24.4 ± 1.3</td>
<td>24.5 ± 1.4</td>
<td>24.3 ± 1.3</td>
<td>24.4 ± 1.1</td>
<td>24.7 ± 1.3</td>
</tr>
<tr>
<td>Famotidine</td>
<td>24.4 ± 1.7</td>
<td>24.5 ± 1.2</td>
<td>24.5 ± 1.1</td>
<td>24.5 ± 1.0</td>
<td>24.5 ± 1.0</td>
<td>24.6 ± 1.0</td>
<td>24.6 ± 1.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Anesthesiology, V 83, No 6, Dec 1995
Table 3. Thermoregulatory Thresholds for Vasoconstriction in the Arm and Leg

<table>
<thead>
<tr>
<th>Vasoconstriction Threshold</th>
<th>Forearm-Fingertip Gradient</th>
<th>Calf-Toe Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0°C</td>
<td>4°C</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD. Values in parentheses are the number of patients whose gradients equaled zero and 4°C.

* P < 0.05 versus control group.

temperature through central thermoregulation, not through a hemodynamic effect.

Injection of histamine into the cerebral ventricles or the hypothalamus reportedly induces dose-dependent hypothermia in unanesthetized rats and mice.5,6 Hypothermia, induced by intraventricular injection of H2-agonist, was antagonized by intraventricular injection of cimetidine.7,8 Conversely, intraventricular injection of histamine in anesthetized rats induces hyperthermia, which is antagonized by cimetidine administered either intraventricularly or intraperitoneally.7 Intraventricular injection of histamine in cats causes hypothermia followed by hyperthermia.8 This hypothermic response is prevented by H1-antagonists, and the hyperthermic response is prevented by metiamide, an H2-antagonist. The results of the current study agree with those in anesthetized rats and awake cats, but not with those in awake rats.

H2 receptors located close to the third ventricle play an important role in central thermoregulation.4,7 Famotidine is likely to affect the histaminergic central thermoregulatory pathways, which might be activated by histamine released from brain mast cells induced by thiopental or buprenorphine,13 through the circumventricular organ near the third ventricle, which lacks the blood–brain barrier.

Recent advances in the study of intraoperative thermoregulation have provided an understanding of the mechanism of anesthesia-induced core hypothermia.14,15 However, the role of the histaminergic central thermoregulatory pathways has not been evaluated.

The current study revealed that premedication with famotidine augmented core hypothermia during general anesthesia.

We selected 0.4–0.6% isoflurane with epidural buprenorphine to maintain anesthesia. The isoflurane-induced decrease in the vasoconstriction threshold is dose-dependent24 and thus the two groups should have been equally affected. Premedication with larger doses of famotidine may induce a further decrease in the vasoconstriction threshold and therefore more hypothermia. However, we did not evaluate the dose-dependence of thermoregulatory inhibition induced by famotidine. The peak plasma concentration of famotidine, is attained within 1–2 h and, likely gradually decreased during the study. Thus premedication less than 3 h before induction of anesthesia may be associated with more hypothermia than that seen in our patients.

In summary, famotidine premedication decreased the vasoconstriction threshold approximately 1°C. Consequently, patients receiving famotidine had significantly more hypothermia than those who did not. These data confirm the clinical importance of the core-temperature plateau and suggest that famotidine produces a centrally mediated inhibition of a thermoregulatory control.

References

FAMOTIDINE AND TEMPERATURE


Anesthesiology, V 83, No 6, Dec 1995