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TITLE

INFLUENCE OF GRANISETRON ON THERMOREGULATION DURING EXERCISE IN THE HEAT

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ORIGINAL RESEARCH

Influence of Granisetron on Thermoregulation During Exercise in the Heat

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Background: A NATO project group has an interest in selecting an antiemetic agent that not only is effective in the prevention of emesis induced by chemical agents or radiation exposure but also has minimal, if any, side effects. Granisetron is the second candidate drug of a class of selective serotonin antagonists that has been shown to be an effective antiemetic agent for patients receiving radiation or chemotherapy treatment. The present study was designed to evaluate whether a single 2-mg oral dose of granisetron influenced temperature regulation during exercise in a hot and relatively dry environment. ***Hypothesis:*** Based on our previous findings with the other candidate drug, ondanseton, we hypothesized that granisetron would not influence temperature regulation. ***Methods:*** Nine unacclimatized males performed a drug and placebo trial in a double-blind manner. The sessions involved walking on a treadmill at 4.8 $km \cdot h^{-1}$ with a 2% elevation for a maximum of 3 h at 40°C and 30% relative humidity while wearing combat clothing. ***Results:*** Granisetron was associated with a small (0.2°C) but significant elevation in mean skin temperature at the beginning and after 2 h of exercise. However, there was no difference between trials for the 1.6°C increase in rectal temperature. Also, body heat gain (406 ± 97 and 407 ± 103 kJ for the placebo and drug trial, respectively) and whole body sweat rates (0.72 ± 0.10 and 0.73 ± 0.10 $kg \cdot h^{-1}$ for the placebo and granisetron trial, respectively) were not different. Tolerance times also were not different for the placebo (157.4 ± 16.7 min) and drug (159.4 ± 20.4 min) sessions. ***Conclusions:*** For the environmental conditions used in this investigation, we would accept the null hypothesis that a single 2 mg oral dose of granisetron does not influence temperature regulation during exercise.

THE CANADIAN FORCES together with other NATO countries have an interest in selecting an antiemetic agent that not only is effective in the prevention of emesis induced by chemical agents or radiation exposure, but also has minimal, if any, side-effects. Previously, we reported that the candidate drug ondansetron did not influence the thermoregulatory and cardiorespiratory responses during submaximal exercise in a hot environment (12). A second candidate drug, granisetron (Kytril®), also has been shown to be an effective antiemetic agent for patients receiving chemo- or radiation-therapy (3,8,15,20). Both candidate drugs are selective antagonists for type 3 serotonin ($5\text{–}HT_3$) receptors (1,5). $5\text{-}HT_3$ receptors in the gastrointestinal tract have been implicated in the emesis induced by cytotoxic agents (1).

Based on our previous findings with ondansetron, there would be no overwhelming evidence to suggest that granisetron should influence temperature regulation or the cardiorespiratory response during exercise. Ondanseton was shown to produce a small but significant decrease in ventilation during submaximal exercise but this decrease did not affect the rate of oxygen consumed ($\dot{V}O_2$) or carbon dioxide produced ($\dot{V}CO_2$) (12). In addition, Bruning et al. (2) recently reported that $5\text{-}HT_3$ receptors were not involved in the serotonin-induced increase in human forearm blood flow. Thus, even if serotonin were involved in the active vasodilation of peripheral vascular beds during exercise and heat stress, there would be no reason to expect that granisetron would reduce the magnitude of this vasodilation and, therefore, increase the rate of body heat storage.

The final selection of an antiemetic agent should be based on comparative experimental data. Ideally, both candidate drugs should have been compared with the same subjects under identical experimental conditions. Given the delays in receiving approval for marketed distribution of granisetron in Canada, this candidate drug was not available when our previous experiment was conducted with ondansetron. The present study, therefore, has examined the influence of granisetron on thermoregulatory and cardiorespiratory responses during exercise using different subjects, but environmental conditions similar to our previous experiment (12).

Military operations must be able to be sustained in hot environments. It is well documented that exposure to high ambient temperatures and/or vapor pressures can affect soldiers' physical work capacity (6,10,11,14). Commanding officers must know whether their unit's performance will be affected by the ingestion of any prophylactic agent. As a result, it was the purpose of the present study to examine the influence of a single 2-mg oral dose of granisetron on thermoregulation during exercise in a hot and relatively dry environment. These conditions were selected to reflect recent operational environments and to be consistent with our previous work with ondansetron. We hypothesized that granisetron would not affect thermoregulation during exercise under the conditions studied.

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METHODS

Subjects: Following approval from the institute's human ethics committee, nine unacclimatized males volunteered to participate in the study. Mean values (± S.D.) for age, weight, height, and $\dot{V}O_{2max}$ were 32.7 ± 5.2 y, 80.1 ± 8.4 kg, 1.77 ± 0.06 m, and 47.5 ± 7.6 ml · kg^{-1} · min^{-1}, respectively. They were informed of all details of the experimental procedures and the associated risks and discomforts. After a medical examination to ensure that there were no medical contraindications to their participation in the experiment, each subject gave informed consent prior to the first day of data collection.

Determination of maximal aerobic power ($\dot{V}O_{2max}$): $\dot{V}O_{2max}$ was determined on a motor-driven treadmill using open-circuit spirometry before the series of experiments in the climatic chamber (12). Heart rate (HR) was monitored throughout the incremental test from a telemetry unit (Polar Electro PE3000, Stamford, CT). The heart rate value recorded at the end of the exercise test was considered to be the individual's maximum.

Experimental design: All subjects performed a drug and placebo trial in double-blind random order separated by a minimum of 5 d and a maximum of 15 d. The randomization of the trials was performed by SmithKline Beecham Pharmaceuticals, Inc. Personnel from this company were not involved in the collection of data during the investigation. All trials were conducted in the winter months and performed at the same time of day for a given subject. One hour prior to entering the environmental chamber, subjects ingested two 1-mg capsules of either placebo or the antiemetic agent granisetron. Results from pharmacokinetic studies have shown that the half-life of plasma granisetron varies from 3–7 h in healthy males (21). Each trial involved walking on a treadmill at 1.33 m · s^{-1} (4.8 km · h^{-1}) with a 2% grade in the environmental chamber set at 40°C and 30% relative humidity. All trials continued for a maximum of 3 h or until rectal temperature (T_{re}) reached 39.3°C, heart rate remained at or above 95% of the individual's maximum for 3 min, nausea or dizziness precluded further exercise, the subject asked to be removed from the chamber, or the investigator removed the subject from the chamber. With the exception of the ingestion of the drug or placebo, subjects also performed a familiarization trial that involved all aspects of the experimental sessions and used the same criteria for termination of the trial. This session was performed 1 week prior to the drug and placebo trials.

Dressing and weighing procedures: These procedures have been detailed in our previous study (12). Upon entering the chamber, the subject's skin and rectal thermistor monitoring cables were connected to a computerized data acquisition system (Hewlett-Packard 3497A control unit, 236-9000 computer and 2934A printer, Mississauga, Ontario) and the exercise began. No fluid consumption was allowed during the exposures. The different physiological variables were recorded continuously during the trials and the mean values over 1-min periods were calculated for T_{re} and a 12-point weighted mean skin temperature ($\bar{T}_{sk}$) (12), recorded and printed by the data acquisition system. HR was recorded every 5 min from the display on the telemetry receiver.

Differences in nude and dressed weights before and after each trial were corrected for respiratory and metabolic weight loss (see below). The rate of sweat production was calculated as the difference between the corrected pre-trial and post-trial nude weights, divided by tolerance time, which was defined as the difference in time between removal from and entry into the environmental chamber. Evaporative sweat loss was calculated from the differences in pre- and post-trial corrected dressed weights. The evaporative efficiency represented the evaporative sweat loss expressed as a percentage relative to the total sweat produced.

Gas exchange analyses: During each trial, open-circuit spirometry was used to determine expired minute ventilation ($\dot{V}_E$) and oxygen consumption ($\dot{V}O_2$) using a 2-min average obtained every 15 min. Respiratory water loss was calculated using the $\dot{V}O_2$ measured during the trial and the equation presented by Mitchell et al. (13). Metabolic weight loss was calculated from $\dot{V}O_2$ and the respiratory exchange ratio using the equation described by Snellen (17).

Calculation of body heat content: The body heat gain (HG in kJ) during the heat exposure was calculated for each subject by subtracting the body heat content at thermoneutrality before the trial (HC_N in kJ) from the body heat content at the end of the trial after the heat exposure (HC_H in kJ) as follows:

$$HG = HC_H - HC_N \quad \text{Eq. 1}$$

$$HC_H = (0.90T_{re(f)} + 0.10\bar{T}_{sk(f)}) \cdot m_{b(f)} \cdot 3.47 \quad \text{Eq. 2}$$

$$HC_N = (0.79T_{re(i)} + 0.21\bar{T}_{sk(i)}) \cdot m_{b(i)} \cdot 3.47 \quad \text{Eq. 3}$$

where $0.90T_{re(f)} + 0.10\bar{T}_{sk(f)}$ represents the mean body temperature at the end of the heat exposure (7,16), $T_{re(f)}$, $\bar{T}_{sk(f)}$ and $m_{b(f)}$ represent the final rectal temperature, mean skin temperature and body mass at the end of the trial, respectively, and 3.47 is the average specific heat of body tissues (in kJ · kg^{-1} · °C^{-1}). The mean body temperature at thermal neutrality before the heat exposure was estimated as $0.79T_{re(i)} + 0.21\bar{T}_{sk(i)}$ (4), where $T_{re(i)}$ and $\bar{T}_{sk(i)}$ represent the initial rectal and mean skin temperatures, respectively.

Statistical analyses: Data are presented as mean values and the standard deviation of the mean. A dependent *t*-test was used to evaluate any differences between the placebo and drug trials for sweat production, sweat evaporation, body heat gain and tolerance time. A two-factor (trial and time) repeated measures analysis of variance was performed for evaluating the changes in $\dot{V}O_2$, T_{re}, $\bar{T}_{sk}$ and HR during the exposures. When a significant F-ratio was obtained, a Newman-Keuls post-hoc analysis was used to isolate differences among treatment means. For all statistical analyses, the 0.05 level of significance was used.

RESULTS

Mean tolerance times were not different between trials (**Table I**). Only 2 of the 9 subjects completed the 3 h of walking during both sessions. For the remaining subjects, 3 terminated both trials on their own volition and 3 reached 39.3°C for T_{re} during each session. Individual tolerance times for the 2 trials differed by a maximum

TABLE I. TOLERANCE TIME, RATE OF SWEAT PRODUCTION, EFFICIENCY OF SWEAT EVAPORATION AND BODY HEAT GAIN FOR THE PLACEBO AND GRANISETRON TRIALS DURING TREADMILL WALKING AT 40°C AND 30% RELATIVE HUMIDITY.

	Placebo	Granisetron
Tolerance Time (min)	157.4 ± 16.7	159.4 ± 20.4
Rate of Sweat Production ($kg \cdot h^{-1}$)	0.72 ± 0.10	0.73 ± 0.10
Evaporative Efficiency (%)	79.6 ± 6.9	79.5 ± 6.2
Body Heat Gain (kJ)	406.3 ± 97.2	407.1 ± 103.3

Values are means ± SD; n = 9.

of 20 min, with 6 of the subjects' times differing by less than 10 min.

Granisetron had no influence on the rate of sweat production, the rate of sweat evaporation from the clothing or the thermometric estimate of body heat gain (Table I). Granisetron was associated with a small but significant increase of approximately 0.2°C in $\bar{T}_{sk}$ at 0, 5, 115 and 125 min (Fig. 1). There were no other differences in $\bar{T}_{sk}$ between trials which increased to approximately 37°C. Also, granisetron had no impact on the increase in T_{re} from 37.2°C to 38.8°C (Fig. 2).

There was no difference between trials for $\dot{V}_{O_2}$ which averaged 15.0 ± 0.9 and 15.1 ± 1.1 $ml \cdot kg^{-1} \cdot min^{-1}$ or 223.0 ± 12.6 and 225.2 ± 15.1 $W \cdot m^{-2}$ for the placebo and granisetron sessions, respectively. Ventilation also was not different ($p < 0.15$) between the placebo (25.6 ± 3.5 $l \cdot min^{-1}$, STPD) and granisetron trials (24.7 ± 3.7 $l \cdot min^{-1}$). Finally, granisetron had no influence on the heart rate response, which increased from 97.4 ± 9.3 $b \cdot min^{-1}$ after 5 min of exercise to 150.2 ± 23.1 $b \cdot min^{-1}$ at 135 min (N = 9) for the placebo trial and from 97.2 ± 6.7 $b \cdot min^{-1}$ to 146.9 ± 27.0 $b \cdot min^{-1}$ for the granisetron trial.

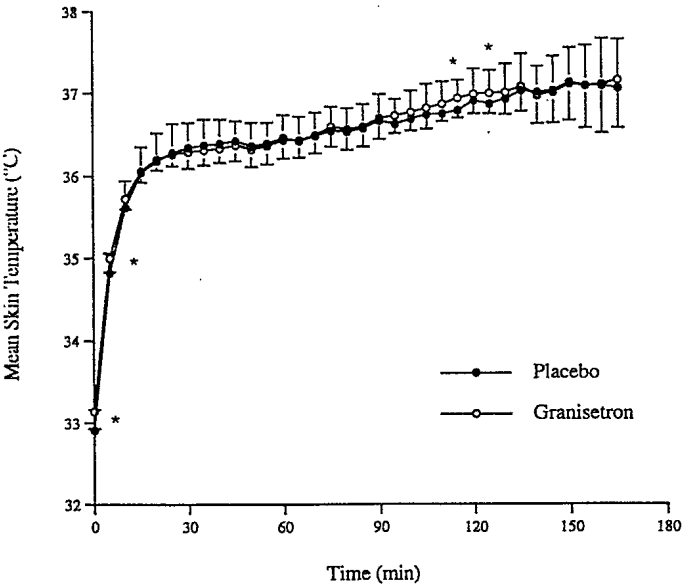

Fig. 1. Changes in mean skin temperature during the treadmill walk at 40°C and 30% relative humidity for the placebo (closed circles) and granisetron (open circles) trials. N = 9 to 135 min; N = 5 to 150 min; N = 4 to 165 min. The asterisk indicates a significant difference between trials at 0, 5, 115, and 125 min.

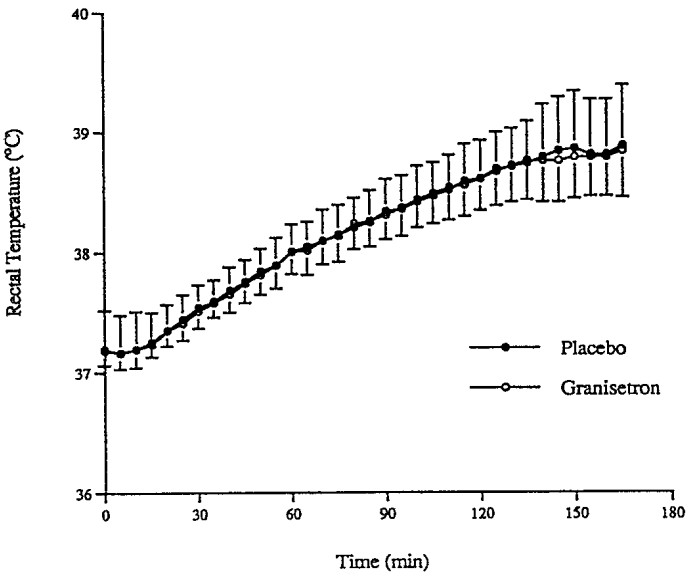

Fig. 2. Changes in rectal temperature during the treadmill walk at 40°C and 30% relative humidity for the placebo (closed circles) and granisetron (open circles) trials. N = 8 to 135 min; N = 4 to 150 min; N = 3 to 165 min.

DISCUSSION

The present study has examined whether a single 2-mg oral dose of the antiemetic agent granisetron influenced the normal cardiorespiratory and thermoregulatory responses during submaximal exercise in a hot environment. Plasma concentrations of granisetron were not measured in the present investigation. However, both the method of administering the drug per os and the total dosage of 2 mg would be considered therapeutic for the prevention of emesis in patients receiving chemo- or radiation-treatment for cancer (1). In addition, pharmacokinetic studies have reported the plasma half-life of granisetron to vary between 3 and 7 h for healthy males (21). Thus the plasma concentrations of granisetron should have remained at a therapeutic level for the duration of the exercise period in this study.

The results of this investigation have provided little or no evidence to suggest that the ingestion of 2 mg of granisetron will influence temperature regulation during exercise in a hot and relatively dry environment. Granisetron was associated with small elevations in $\bar{T}_{sk}$ of approximately 0.2°C at the beginning of the trial and after 115 and 125 min of exercise (Fig. 1). Although changes in $\bar{T}_{sk}$ during exercise do not necessarily parallel changes in skin blood flow (9), the elevations in $\bar{T}_{sk}$ following the ingestion of granisetron may indicate an increased vasodilation in the peripheral circulation. Bruning et al. (2) did report that a 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ arterial infusion of granisetron for 10 min (this represents a total dose of approximately 0.75 mg for their subjects) was associated with a 40% increase in resting forearm blood flow in room temperatures of 23°C. Therefore, the small increases in $\bar{T}_{sk}$ observed at the beginning of our exercise trials may reflect an initial elevation in peripheral blood

flow 1 h following the ingestion of the 2 mg dose of granisetron. Whether a similar mechanism might account for the different $\bar{T}_{sk}$ after approximately 2 h of exercise is not known. Certainly it would appear that those factors involved in the control of peripheral blood flow during exercise in the heat (for review see 9) were not affected by the drug during the majority of the exposure in the environmental conditions selected for this investigation. Although it would have been of interest to measure and correlate skin blood flow with the differences in $\bar{T}_{sk}$ between trials, it is unlikely that the small differences in $\bar{T}_{sk}$ that were observed for such short periods of time had any effect on heat storage. Indeed our thermometric estimate of heat storage was not different between trials (Table I). In addition, whole body sweat rates and T_{re} were not influenced by the ingestion of granisetron (Table I and Fig. 2). Finally, the cardiovascular strain of the heat stress, as indicated by heart rate, was not affected by the ingestion of the drug. We would accept the null hypothesis, therefore, that the ingestion of 2 mg of granisetron does not influence the thermoregulatory response to exercise in a hot environment. A similar finding was reported under similar conditions for the other candidate drug, ondansetron (12). Thus there would be no reason to favor the selection of one of the drugs based on the thermoregulatory responses in the present study and our previous work.

The ingestion of granisetron also did not affect the cardiorespiratory response to the exercise in the hot environment as indicated by the similar values for $\dot{V}_{O_2}$, $\dot{V}_E$ and heart rate between trials. The drug was associated, however, with a nonsignificant reduction in $\dot{V}_E$. Our previous findings with ondansetron did reveal a small but significant reduction in $\dot{V}_E$ towards the end of the exercise session. We estimated that these small reductions would have produced only a minor increase in arterial blood P_{CO_2} since $\dot{V}_{CO_2}$ and tidal volumes were not affected by the drug (12). We would conclude, therefore, that there also would be no reason to prefer one of the candidate drugs based on the cardiorespiratory responses during light exercise.

Neither the present study, nor our previous work, have examined the possible interactions of granisetron or ondansetron with other prophylactic agents, such as pyridostigmine bromide, which could be administered during the same time period. This latter drug is known to reduce skin blood flow and increase sweat rate during moderate exercise approximating 330 $W \cdot m^{-2}$ in a warm (29°C) environment (18). It would be relevant to examine the interactive effects of the therapeutic doses of the 5-HT_3 antagonists and pyridostigmine bromide on skin blood flow and body heat storage.

It would also be of interest to examine the impact of the antiemetic agents on temperature regulation under conditions where evaporative heat exchange is restricted and the reliance on dry heat flux is increased. Under these conditions, it is possible that an increased $\bar{T}_{sk}$ resulting from the ingestion of the antiemetic agent may delay the increase in body heat storage. It is noteworthy that elevated skin temperatures and forearm skin blood flow following the ingestion of niacin have been associated with lower esophageal temperatures during moderate treadmill exercise while wearing chemical protective clothing in ambient temperatures of 28°C (19).

In summary, the present study has revealed that a single 2-mg oral dose of granisetron has a minor influence on mean skin temperature during exercise in a hot and relatively dry environment. The small changes in mean skin temperature that were observed following the ingestion of the drug, however, did not influence rectal temperature or our thermometric estimate of body heat storage. Also, granisetron had no effect on the cardiorespiratory response to the exercise challenge in the hot environment.

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