# The Effect of Ibuprofen on Thermoregulatory Responses and Gastrointestinal Distress to Exercise in Hot Environments

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## ABSTRACT

Ibuprofen, a commonly used nonsteroidal anti-inflammatory drug (NSAID) among athletes to alleviate pain and inflammation during exercise, is hypothesized to mitigate exercise-induced increases core temperature (Tc) and improve heat tolerance during exercise in hot environments. However, its prophylactic use specially during exercise associated with heat stress may lead to harmful effects specifically inducing gastrointestinal complications such upper-GI bleeding. **PURPOSE:** To investigate the effect of ibuprofen on thermoregulatory responses and the occurrence of gastrointestinal symptoms to exercise in a hot environment. **METHODS:** In a double-blind, randomized, counterbalanced cross-over design, 6 endurance trained males and females (n=12) completed 60-minutes of treadmill running at moderate intensity [65% of maximum oxygen consumption ($VO_2max$)] on two separate occasions. Ibuprofen (1200 mg total) or PL were administered by two capsule ingestions at 12 hours and 60 minutes prior to each trial. Throughout the exercise trials, core temperature using a rectal thermistor, and heart rate (HR) via chest strap was recorded every 5 minutes. Ratings of perceived exertion (RPE) (Borg, 1982), thermal sensation, thermal comfort, and GI symptoms were asked and recorded every 10 minutes of exercise. Urine specific gravity (USG) was measured using a refractometer pre and post trials to determine euhydration **RESULTS:** Tc and HR increased over time during both experimental trials but no significant differences were observed for peak TC and HR (39.01±0.50 P=<2e-16, 172.35±15.17 P=0.232, respectively) between the two groups. There were no significant differences observed between groups in maximum RPE (15.67±1.99 P=0.391), maximum Ts (7.38±0.49 P=0.293), and maximum thermal comfort (3.38±1.06 P=0.397). No differences between groups were found for GI symptoms. **CONCLUSION:** In summary, our study demonstrates that ibuprofen, when administered with maximum dosage for over counter usage, does not have detrimental effect on GI distress or thermoregulatory responses during exercise in hot conditions.

**INTRODUCTION**

Ibuprofen, a widely used nonsteroidal anti-inflammatory drug (NSAID), is commonly employed to alleviate pain and inflammation. It functions by inhibiting two cyclooxygenase isoforms (COX-1 and COX-2) which regulate gastric mucosa, platelet aggregation, renal blood flow, and the production of inflammatory mediators that contribute to pain, inflammation, and fever (Emerson et al., 2021). Athletes may prophylactically take ibuprofen prior to training sessions or competition to prevent pain and inflammation from occurring and potentially improve performance (Warden, 2010). A recent systematic review by Emerson et al. (2021) presented the controversies as to whether the use of ibuprofen may also mitigate increases in core temperature (Tc) during exercise. Although exercise-induced hyperthermia is not driven by pyretic factors, it is hypothesized that inflammation can impact Tc responses and therefore, ibuprofen may lower Tc by eliciting an anti-inflammatory response through prostaglandin inhibition during exercise (Emerson et al., 2021). This in turn could increase heat tolerance during exercise by mitigating hyperthermia and the overall inflammatory response (Emerson et al., 2021). Nonetheless, Emerson et al. (2021) identified two studies reporting no significant effects on Tc when ibuprofen was used during exercise in hot environment. However, these studies were not conducted in runners and thermoregulatory responses were not measured. Additionally, in the study by Farquhar et al. (1999), the authors manipulated salt ingestion and dehydration which may have interfered with thermoregulatory responses and consequently, Tc.

While ibuprofen may have these beneficial effects, caution is warranted with prophylactic use as ibuprofen may lead to harmful effects specifically inducing gastrointestinal complications such as benign dyspepsia and esophagitis, which may lead to upper-GI bleeding (Emerson et al., 2021; Warden, 2010). Additionally, evidence suggests that prophylactic ibuprofen use increases GI permeability during exercise; although this is not fully understood (Warden, 2010). Speculations have been made that ibuprofen may reduce local nitric oxide production affecting vasodilation and blood flow in the GI tract. Strenuous and prolonged exercise in hot conditions induce increases in Tc associated with increasing blood flow to the skin, potentially reducing blood flow to the GI system which may cause GI ischemia. Additionally, elevated Tc may also affect cell function and affect cell-wall permeability, leading to increased gut permeability and the passage of endotoxin and pathogens into the systemic circulation, resulting in

endotoxemia. In fact, a study reported that 81% of marathon runners with Tc of 42°C exhibited elevated endotoxin levels, and of these individuals, 80.6% reported GI illnesses such as nausea, vomiting and/or diarrhea compared with 17.7% with low endotoxin values (Brock-Utne, 1988).

While taking ibuprofen prior to an endurance event in hot conditions may theoretically reduce Tc, its effects on GI distress symptoms remains unclear. Additionally, ibuprofen may exacerbate the severity of GI damage during exercise in hot environments (Van Wijck et al., 2012). Therefore, further investigation into the effects of ibuprofen use during exercise in hot environments is essential to better educate and prepare athletes for performance and health in the heat.

**PURPOSE**

The purpose of this study was to investigate the effect of ibuprofen on thermoregulatory responses and the occurrence of gastrointestinal symptoms to exercise in a hot environment.

**DESIGN/METHODS**

In a double-blind, randomized, counterbalanced, cross-over design, twelve healthy, endurance-trained males [n=6; age=30.3±7.2 years, height=182.4±2.8 cm, body weight (BW)=79.7±10.6 kg, body fat (BF)=14.4±6.1 %, maximal oxygen consumption ($VO_2max$)=51.8±6.2 ml/kg/min] and females (n=6; age=32±3.7 years, height=166.7±7.4 cm, BW = 60.4±5.2 kg, BF=15.9±9.5 %, $VO_2max$=49.8±8.0 ml/kg/min), were recruited locally via word of mouth for participation in this study. Written consent was obtained from all participants, and the study was approved by the University of New Mexico's Institutional Review Board (IRB).

*Baseline assessment:* The initial visit was comprised signing the informed consent followed by baseline measurements. These measurements included height, BW, and body composition assessment by bioelectrical impedance (InBody520). Subsequently, a maximal graded treadmill exercise test to determine maximum oxygen consumption ($VO_2max$) was completed. Upon completion, the treadmill speed that corresponded to 65% of $VO_2max$ was identified and used as the exercise intensity during the subsequent experimental exercise trials in the heat chamber. A metabolic cart was used to perform identify the $VO_2max$ and the exercise intensity at 65% of $VO_2max$.

*Experimental Trials:* Two additional visits (visits two and three) involved participants performing 60-minutes of running on a treadmill at their pre-determined workload in a heat chamber set at 35°C and 20-

40% humidity. Each participant completed the two exercise trials, separated by 7 days: one with ibuprofen, and one with ingestion of 600 mg of ibuprofen and the other with a placebo (PI). Ibuprofen or PL were administered by two capsule ingestions at 12 hours and 60 minutes prior to each trial. Participants were provided a standardized breakfast to consume 2 hours prior to each trial.

Upon arrival, Urine specific gravity (USG) was measured using a refractometer to determine euhydration (USG <1.020) (*ACSM's guidelines for exercise testing and prescription*, 2018). Urine flow rate was then measured for 1 hour. Pre-exercise nude body weight was recorded, and venous blood samples were collected via venipuncture. Blood samples were processed and frozen at -81°C freezer for subsequent analysis. Then, the subjects entered in the environment chamber and start performing the 60-minutes of running in the environmental chamber. Throughout the exercise trials, core temperature was monitored every 5 minutes using a rectal thermistor, and heart rate (HR) was continuously recorded via chest strap, also at 5 minutes intervals. Ratings of perceived exertion (RPE) (Borg, 1982), thermal sensation, and thermal comfort were asked and recorded every 10 minutes. A modified analogue scale to measure Upper GI, lower GI, overall gut discomfort, nausea, dizziness, and abdominal stitch GI symptoms was administered at minute 30 during exercise, post-, and 1-hour post-exercise (Gaskell et al., 2019). Upon exercise cessation, participants voided their bladder, obtained nude body weight then rested for 10 minutes, at room temperature, followed by a post-exercise blood sample collection. Water was then provided, and urine flow rate was measured for 1-hour post-exercise. A final 1-hour post-exercise blood and urine sample were collected.

*Statistical Analysis:* Statistical analyses were performed using R Studio. Core temperature at baseline and every 10-minutes during exercise, as well pre- and post-exercise BW, and pre-, post-, and 1-hour post-exercise USG were analyzed using a two-way ANOVA (condition [placebo vs. ibuprofen] x time). Upper GI, lower GI, overall gut discomfort, nausea, dizziness, and abdominal stitch GI symptoms at minute 30, post-, and 1-hour post-exercise were analyzed using a two-way ANOVA. Additionally, a one-tailed paired *t*-test was used to assess between-group differences in peak Tc, maximum RPE, thermal sensation (Ts), thermal comfort, and HR, and pre- post-exercise urine volumes. An $\alpha$ level of ≤0.05 was used to determine statistical significance and data is presented as mean±standard deviation (SD).

**RESULTS**

During both experimental trials, there was an increase in Tc recorded at 10-minute intervals over time (P=<2e-16). However, there were no significant differences in Tc between the two groups in any time point (P=0.994) or peak Tc (P=0.323) (Placebo: 39.05±0.48; Ibuprofen: 38.97±0.54). Additionally, there were no significant differences between groups in maximum RPE (P=0.391) (Placebo: 15.7±2.3; Ibuprofen: 15.6±1.7), maximum Ts (P=0.293) (Placebo: 7.4±0.5; Ibuprofen: 7.3±0.5), maximum thermal comfort (P=0.397) (Placebo: 3.3±1.2; Ibuprofen 3.4±0.9), and maximum HR (P=0.232) (Placebo: 173±14; Ibuprofen: 171±15).
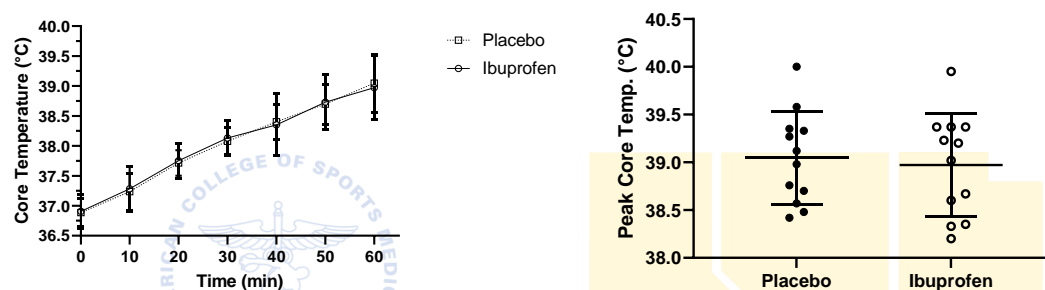


On a scale of 0-10 (0-3=very mild symptoms; 4-6=severe symptoms; and 7-10=very severe symptoms) upper GI, lower GI, overall gut discomfort, nausea, dizziness, and abdominal stitch GI symptoms were analyzed at minute 30, post-, and 1-hour post-exercise. No significant differences in upper (P=0.127), lower (P=0.536), and overall GI symptoms (P=0.303) when comparing groups and time points. No significant differences in nausea (P=0.254), dizziness (P=0.516) and abdominal stitch (P=0.926) were found when comparing groups and time points. Additionally, no significant differences were found between groups in %change BW (P=0.364) (placebo: -2.64±0.94; ibuprofen: -2.68±0.68).

No significant differences were found between groups in pre-exercise urine volumes (P=0.338) (placebo: 454±185; ibuprofen: 428±235). There were also no significant differences found between groups in post-exercise urine volumes (P=0.493) (placebo: 72±65; ibuprofen: 72±67).

Significant differences were found within the placebo group from pre- to 1-hour post-exercise USG (P=0.0019) (pre: 1.010±0.01; 1-hour post: 1.020±0.01, respectively). There was also a significant difference found in USG pre- to 1-hour post-exercise (P=0.00043) (pre: 1.010±0; 1-hour post: 1.020±0.01) and pre- to post-exercise (P=0.04196) (post: 1.010±0.01) within the ibuprofen group.

**DISCUSSION**

The purpose of this study was to investigate whether ibuprofen would have an effect on thermoregulatory responses and/or GI symptoms during exercise in a hot environment. Our findings indicate that the administration of 600 mg of ibuprofen, taken 12-hours and 1-hour prior to a moderate-intensity exercise bout in a hot environment, did not induce any significant differences compared to placebo in core temperature, dehydration, perceived exertion, thermal comfort, and heart rate. Furthermore, ibuprofen did not increase GI symptoms compared to placebo.

Ibuprofen is thought to have an effect on Tc responses during exercise by attenuating the inflammatory response typically associated with exercise (Emerson et al., 2021). However, this theory was not supported in the present study as our results indicates no differences in Tc between the ibuprofen and placebo trials. These results are similar to Farquhar et al. (1999) who also did not find an effect in Tc. Therefore, consuming 600mg of ibuprofen 12 hours and 1 hour before exercise does not mitigate increases in Tc during exercise in hot environments.

It is possible that the ibuprofen dosage and timing of consumption was not sufficient to induce a significant effect. In this study, we used the maximum dosage of Ibuprofen for over-the-counter usage, but prescription up to 3,200 mg per day can be used with physician's prescription. According to Emerson et al. (2020), higher doses of ibuprofen (1200 mg) are recommended to elicit an anti-inflammatory and analgesic effect as there is less COX-2 selectivity and shorter half-lives. Also, an increased consumption time (i.e., more than 24 hours) may be needed to observe significant effects. This was demonstrated in a study by Gilbert (1996) where chronic aspirin use affected negatively RPE, lactate, hematocrit, and fatigue during exercise.

Although the mechanisms for GI distress during exercise, particularly in hot conditions, is not fully understood, it is suggested to be related to GI ischemia-reperfusion and inflammatory responses (Emerson et al., 2020; Garden & Granger, 2000; Jeukendrup et al., 2000). Furthermore, ibuprofen is known to induce GI side effects and is suggested that ibuprofen use during exercise in hot environments specifically, could potentially exacerbate GI distress (Van Wijck et al., 2012). In the present study, we did not find that ibuprofen significantly increased GI distress symptoms compared to placebo. This finding is similar to the findings by Emerson et al. (2020) who also did not find any significant increases in GI symptoms with the use of Naproxen during a 90-minute cycling exercise trial in a hot environment.

However, these authors used a much lower NSAID dose of 250mg and participants consumed this 24 hour prior to their exercise trial.

**CONCLUSIONS**

In summary, our study demonstrates that ibuprofen, when administered with maximum dosage for over counter usage, does not have detrimental effect on GI distress or thermoregulatory responses during exercise in hot conditions.
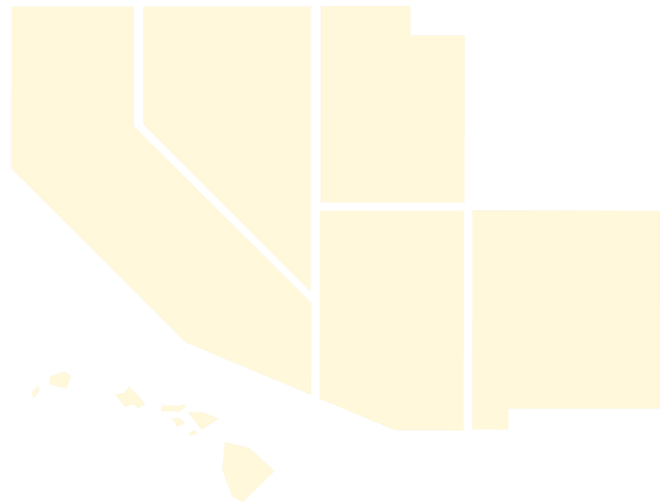
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