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Original Research

A 24 hour naproxen dose on gastrointestinal distress and performance during cycling in the heat

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ABSTRACT

Using a double-blind, randomized and counterbalanced, cross-over design, we assessed naproxen's effects on gastrointestinal (GI) distress and performance in eleven volunteers (6 male, 5 female). Participants completed 4 trials: 1) placebo and ambient); 2) placebo and heat; 3) naproxen and ambient; and 4) naproxen and heat. Independent variables were one placebo or 220 mg naproxen pill every 8 h (h) for 24 h and ambient (22.7 ± 1.8°C) or thermal environment (35.7 ± 1.3°C). Participants cycled 80 min at a steady heart rate then 10 min for maximum distance. Perceived exertion was measured throughout cycling. Gastrointestinal distress was assessed pre-, during, post-, 3 h post-, and 24 h post-cycling using a GI index for upper, lower, and systemic symptoms. No statistically significant differences occurred between conditions at any time for GI symptoms or perceived exertion, distance, or heart rate during maximum effort. A 24 h naproxen dose did not significantly affect performance or cause more frequent or serious GI distress when participants were euhydrated and cycling at moderate intensity in a thermal environment.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) decrease pain and inflammation by inhibiting cyclooxygenase (COX). COX-1 is constitutively expressed to maintain renal blood flow, platelet aggregation, and gastric mucus secretions, while COX-2 is upregulated in response to trauma/illness and produces pain, inflammation, and fever.[1] Due to differing chemical structures and ingredients, each NSAID varies in its mechanism of action, dosage, and effectiveness. For example, aspirin has greater COX-1 selectivity, making aspirin effective at reducing cardiovascular events (e.g., blood clots) but less effective at reducing moderate to severe pain and inflammation.[2,3] Comparatively, naproxen is more COX-2 selective, meaning it is less effective at reducing cardiovascular events but more effective on pain and inflammation.[2]

Physically active individuals use prescription and over-the-counter NSAIDs prophylactically or as treatment following injury in order to "continue playing".[4–8] NSAIDs are perceived to improve performance by mitigating pain and fatigue,[6] which would subsequently improve time to exhaustion, number of maximum repetitions, or other objective physiological (e.g., blood lactate, creatine kinase) and subjective (e.g., rate of perceived exertion [RPE], pain score) performance variables. Existing literature regarding NSAID use in sport is conflicting and primarily focuses on aspirin, males, and short, intense exercise bouts in ambient environments.[9–12] A low aspirin dose (10 mg kg^{-1} of body weight) 1 h (h) before maximum lower extremity resistance exercises increased RPE and perceived leg pain compared to placebo.[11] A 20 mg kg^{-1} aspirin dose 1 h before exercise did not significantly affect power output, RPE, heart rate (HR), or alleviate muscle pain during a ramped maximum exertion cycling protocol.[10] A 975 mg aspirin dose 1 h before maximal graded treadmill runs significantly increased RPE,[9] and a 1200 mg ibuprofen dose 1 h before treadmill running did not improve time to exhaustion or RPE and resulted in no significant change to HR.[12] Acute NSAID use, particularly aspirin and ibuprofen, appears to have little effect on performance and, in some instances, may degrade it.

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In addition to potential negative performance effects, NSAIDs are known to cause perforations, hemorrhaging, and increased epithelial permeability along the gastrointestinal (GI) tract.[13–15] As a result of direct GI damage, and exacerbated by stress, fatigue, diet, and a number of other factors (e.g., health status, medication use), individuals may experience subjective GI distress symptoms such as nausea, cramping, diarrhea, etc.[16–18] Furthermore, NSAIDs increase cardiovascular strain by inducing vasoconstriction and increasing peripheral and renal blood vessel pressure.[19] Presumably, NSAID driven effects on the GI and cardiovascular systems could decrease performance. Among male ultra-distance runners, a 400 mg ibuprofen dose 15 min prior to a 42 km trail race (and an additional dose 5 h into the race) resulted in no significant differences in cardiovascular measures or overall perceived pain scores post-race compared to control.[20] Two 325 mg aspirin doses or 2–200 mg ibuprofen doses 24 h prior to a 1 h treadmill run in a thermoneutral environment elicited no significant differences in HR, RPE, or GI symptoms.[15]

Due to differing mechanisms of action and COX selectivity, it is important to study non-aspirin NSAIDs, such as naproxen, on performance and GI distress. Further, there is a lack of literature on physiological and perceptual responses in thermal environments with longer exercise sessions and including females. This research was part of a larger study examining naproxen's effects on thermoregulation, inflammation, GI damage, and hydration-electrolyte balance, which can all impact performance and perceived GI distress symptoms. The primary aim of this study was to determine the effects of an acute, over-the-counter naproxen dose on GI distress symptoms and performance during moderate-intense cycling in a thermal environment. We hypothesized naproxen would induce significantly more GI distress and decrease performance compared to placebo controls and that these effects would be exacerbated with heat stress.

Materials and methods

We utilized a double-blind, randomized and counter-balanced, crossover design. Participants completed 4 conditions: 1) placebo and ambient (Control); 2) placebo and heat (Heat); 3) naproxen and ambient (Npx); and 4) naproxen and heat (NpxHeat). A minimum of 7 days rest separated each trial to ensure there were no residual naproxen or exercise effects prior to the next trial. All trials took place in an environmental chamber (thermal = 35.7 ± 1.3°C, 53.2 ± 3.2% relative humidity) or laboratory (ambient = 22.7 ± 1.8°C, 52.4 ± 5.5% relative humidity). A 24 h dose (3 capsules) of placebo (cellulose) or naproxen sodium was given to participants before data collection. The 24 h dose was similar to previous research examining GI effects.[15,21,22] A local pharmacy compounded the capsules to look the same to blind participants and primary investigators to whether a trial was naproxen or placebo. Each naproxen pill contained 220 mg of naproxen sodium, the dose found in over-the-counter Aleve®. A research assistant randomized participants into a trial order and prepared capsules in coded, sealed envelopes. Participants consumed 1 capsule at 16 h, 8 h, and 0 h before data collection. All participants were given specific take-home instructions to follow 24 h before data collection. Directions for taking each capsule (i.e., timing and taking with at least 8 oz of fluid and not with food) were based on manufacturer directions for over-the-counter Aleve® and were intended to maximize potential naproxen induced GI effects. Dependent variables included HR, RPE, distance covered during a 10 min time trial, perceived GI distress symptoms, and GI bleeding. Measures were assessed pre-, during, post- and 3 h post-cycling.

Participants

Seventeen participants (12 males, 5 females) were recruited from the university and local community. Attrition occurred due to the study's intensity ($n = 2$), time commitment ($n = 3$), and a non-study related injury ($n = 1$). The final sample size was 11 participants (6 male, 5 female; age = 27.8 ± 6.5 years, weight = 79.1 ± 17.9 kg, height = 177 ± 9.5 cm, and VO_{2max} = 41.4 ± 5.7 ml kg^{-1}·min^{-1}). Participants signed an Institutional Review Board approved informed consent form. To be included in the study, participants had to be between 18-35 years old and not currently taking prescription or non-prescription anti-inflammatory or pain medication. Potential participants completed a health and injury history questionnaire and were excluded if they had cardiovascular, respiratory, metabolic, GI, swallowing, or fluid-electrolyte balance disorders or musculoskeletal disorders preventing exercise. Females were asked additional questions about menstrual cycle to identify menstrual regularity and oral contraception use. Potential participants then completed a graded cycling VO_{2max} test and were included in the study if they met the criteria for being recreationally active (male VO_{2max} between 35-40 mL kg^{-1}·min^{-1}; female between 32-40 mL kg^{-1}·min^{-1}).[23] Once included in the study, participants were familiarized with the online diet and activity log and instructed not to take any analgesic or anti-inflammatory medications or use any treatments (e.g., ice or other pain/inflammation relieving techniques) during the study.

Procedures

Cycle exercise protocol

Participants completed a 98 min cycling protocol on a stationary bike (Monark Ergomedic 828E, Monark Exercise AB, Vansbro, Sweden). The bike was calibrated according to the manufacturer's directions prior to data collection. During the information session, the VO_{2max} test was conducted on the same stationary cycle to familiarize individuals to the bike, to working at maximum effort, and to establish the seat and handlebar arrangement to ensure the same set-up was done for each experimental trial.

Participants began with a 3 min warm-up followed by cycling 80 min at a steady HR equivalent to 70% VO_{2max}.[24] To assess performance, the final 10 min mimicked a "time trial" where participants cycled at maximum effort. Participants received verbal encouragement from researchers throughout the entire 10 min. For additional motivation, the top 5 mileages completed during the 10 min were posted on a board in the laboratory and researchers encouraged participants to try to "get on the board" or beat a certain mileage. The cycling protocol concluded with a 5 min cool down.

Rate of perceived exertion (RPE)

The Borg Scale measured participants' RPE pre-, every 15 min during the 80 min steady state, and at 90 min.

Cardiovascular

To ensure participants remained at safe limits and help maintain target HR during 80 min steady state cycling, HR was continuously monitored and recorded every 5 min using Polar HR monitors (Polar Electro Inc., Lake Success, NY). To determine effects on performance, maximum HR was measured at the end of the 10 min maximum effort.

Core temperature (Tc)

Due to the larger study and to ensure participants remained at safe levels during exercise, Tc was monitored using rectal thermometry (Doric 450 Series digital thermometer, VAS Engineering, Inc., San Diego, CA). Participants were not allowed to exceed 40°C.

Gastrointestinal distress

Fecal occult blood (FOB) was measured using guaiac-based take-home kits (Fisher HealthCare™ Sure-Vue™ Fecal Occult Blood Slide Tests System, Thermo Fisher Scientific Inc., Waltham, MA). By measuring heme-, guaiac-based FOB has high specificity for detecting blood from any portion of the GI tract (i.e., stomach, small intestine, and/or colon). Participants were provided written and verbal instructions (based on the manufacturer's directions) for collecting fecal samples. For each

experimental trial, participants provided the first stool sample after initiating naproxen/placebo and the first stool sample following the exercise protocol. Kits were returned to the investigators on the day of the second sample and immediately analysed following the manufacturer directions.

The GI symptom index was developed based on a previously designed questionnaire[25,26] and is divided into 3 sections: 1) upper abdominal problems (heart burn, reflux, belching, bloating, stomach pain/cramping, nausea, vomiting); 2) lower abdominal problems (intestinal/lower abdominal pain/cramping, flatulence, urge to defecate, side aches/stitch, loose stool, diarrhea); and 3) systemic problems (dizziness, headache, muscle cramps, urge to urinate).[25] Symptoms are scored on a 10-point scale (0 = no problems at all and 9 = the worst it has ever been). A score >4 was considered "serious".[26] Questionnaires were administered pre-, post-, 3 h post-, and at the time of the post-exercise fecal sample (~24 h post-exercise).

Utilizing the above mentioned GI symptom index, a scale was developed to determine upper, lower, and systemic GI symptoms during exercise. Participants were asked every 15 min "Are you currently experiencing GI symptoms?" If the participant answered "yes", they were asked to verbalize the symptom and rank the severity on a 10-point scale (0 = no problems at all and 9 = the worst it has ever been).

Hydration measures

Participants were required to be euhydrated before data collection. Hydration status was determined using a urine sample at pre-, post-, and 3 h post-exercise. A handheld clinical refractometer (model REF 312, Atago Company Ltd., Tokyo, Japan) measured urine specific gravity (Usg); euhydration was defined as ≤ 1.020.[27] To maintain hydration during exercise, participants were required to drink a minimum of 3.5 ml kg^{-1} of water every 15 min; participants could drink more fluid if they desired. Total fluid volume consumed during exercise was recorded. Participants consumed water ad libitum during the 3 h rest after exercise and fluid volume was recorded.

Diet and activity logs

To control potential effects on GI distress and performance, participants self-reported diet and physical activity for 3 days before and 1 day after data collection using the online nutrition software FoodProdigy™ (ESHA Research, Salem, OR). Participants were asked to mimic dietary and physical activity habits during the 24 h before each data collection session. Additionally, participants were instructed to refrain from eating red meat for 3 days before and 1 day after due to the potential to skew FOB tests.

Pre-data collection

Participants received email instructions for completing the diet and physical activity log 72 h before data collection. Participants were instructed to refrain from intense, vigorous exercise 48 h before.[28] Twenty-four hours before, participants received written directions for taking 2 capsules (placebo or naproxen) and reminders for diet, hydration, and activity. To ensure food passed through the stomach before data collection, participants were instructed to consume a small meal at least 2 h before arriving at the laboratory.

Data collection session

Upon arriving at the laboratory, participants were asked if they ingested their 2 pills then instructed to take their third pill. Participants provided a urine sample and voided their remaining urine into the toilet. Baseline Usg was measured to ensure participants were euhydrated. Participants received a HR monitor and the cycling protocol began. Every 15 min, a research assistant asked participants their RPE and GI symptoms. Heart rate and distance travelled during the final 10 min was recorded and participants were asked their RPE and GI symptoms. Following a 5 min cool down on the bike, participants completed a post-GI symptom index and provided a urine sample. The larger study required participants rest 3 h in a semi-reclined/seated position in an ambient environment (23°C, 56% RH). During the rest period participants consumed water ad libitum and received a non-sucrose snack (crackers and wafers) based on body weight, which was the same for each trial. Dependent variables were measured at the end of the rest period.

Statistical analysis

IBM SPSS Statistics (version XV; IBM Corporation, Armonk, NY) was used for all analyses. Descriptive statistics (mean and standard deviations) were calculated for demographics and dependent variables. Using G*Power (version 3.1.9.2, Heinrich Heine University, Dusseldorf, Germany),[29] post-hoc power calculations with means and variances for maximum HR and distance indicated a statistical power > 0.9. Significance level was set at $p < 0.05$ for all analyses.

Dietary (e.g., calories, protein), distance, maximum HR, and Usg were assessed using one-way ANOVA. A 4 (condition) x 8 (time) repeated measures ANOVA determined RPE differences. Because RPE violated sphericity, Greenhouse-Geisser corrections were used. Post-hoc analysis was conducted for significant effects with Bonferroni corrections. Freidman's ANOVA identified differences in GI symptoms between and within conditions. Questions were sectioned into upper, lower, and systemic symptoms to reduce multiplicity; responses were averaged and analysed. Post-hoc analysis was conducted using pairwise comparisons with Bonferroni corrections. Frequency for each GI symptom was calculated to determine percent incidence. Chi-square analysis determined differences in percent of symptoms scored >4 (considered "serious") between conditions and across time. To control for other factors that may influence GI symptoms, Spearman's rho correlations were run for maximum HR, maximum RPE, and distance. Specific Tc results are not presented as part of this study and hydration results are published elsewhere[30]; spearman's rho correlations were conducted for GI symptoms to Tc at the end of the 10 min maximum effort and fluid volume during exercise to determine potential effects.

Results

Participants began experimental trials euhydrated (mean Usg = 1.012 ± 0.005) and maintained euhydration throughout exercise (1.011 ± 0.008) and recovery (1.007 ± 0.006). Diet analysis indicated no significant differences between conditions for calorie, fat, protein, carbohydrate, or sodium intake. No significant differences in exercise (calories burned) 24 h before data collection existed, with all participants maintaining sedentary to low activity. There was no significant difference for mean Tc at 90 min (overall = 38.2 ± 0.3°C) or fluid volume (overall = 1.5 ± 0.7 L) during exercise between experimental conditions.

Performance

Table 1 shows distance, RPE, and maximum HR during 10 min maximum effort for each condition. There was an overall significant main effect ($F_{2.8,110.3} = 163.3$, $p < 0.001$) for increased RPE over time, but no significant differences between conditions. Distance and maximum HR were not significantly different between conditions (Table 2).

Table 1
Performance measures during cycling for experimental conditions (M ± SD).

	Control	Heat	Npx	NpxHeat
Distance (miles)	3.2 ± 0.8	2.9 ± 0.8	3.3 ± 0.8	2.8 ± 0.8
Max HR (bpm)	175.7 ± 14.2	177.8 ± 18.2	176.2 ± 15.0	179.0 ± 18.0
RPE				
Pre	8 ± 2	9 ± 3	9 ± 3	8 ± 2
80 min	13 ± 2	12 ± 2	13 ± 3	12 ± 2
Post	19 ± 2	18 ± 2	19 ± 2	19 ± 2

No significant differences between conditions.

Table 2
Mean and maximum gastrointestinal symptom scores for experimental conditions.

Symptoms	Control		Heat		Npx		NpxHeat	
	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)
Upper								
Reflux/Heartburn	0%	–	2.3%	6 (0.1 ± 0.9)	0%	–	0%	–
Belching	4.5%	1 (0.1 ± 0.4)	4.6%	6 (0.2 ± 0.9)	0%	–	4.5%	4 (0.1 ± 0.6)
Bloating	6.8%	5 (0.4 ± 1.2)	6.8%	6 (0.5 ± 1.3)	11.4%	2 (0.2 ± 0.4)	4.5%	2 (0.2 ± 0.8)
Stomach pain	11.4%	2 (0.3 ± 0.6)	9.1%	6 (0.4 ± 1.3)	6.8%	2 (0.2 ± 0.5)	6.8%	2 (0.3 ± 1.1)
Vomiting	0%	–	4.5%	2 (0.2 ± 1.1)	0%	–	4.5%	2 (0.2 ± 1.1)
Nausea	9.1%	3 (0.2 ± 0.5)	13.7%	6 (0.5 ± 1.4)	2.3%	1 (0.0 ± 0.2)	11.4%	3 (0.3 ± 1.2)
Lower								
Intestinal cramps	13.6%	2 (0.3 ± 0.7)	6.8%	8 (0.5 ± 1.6)	2.3%	1 (0.0 ± 0.2)	4.5%	2 (0.2 ± 1.2)
Flatulence	13.6%	3 (0.3 ± 0.8)	11.4%	4 (0.3 ± 0.9)	6.8%	2 (0.1 ± 0.5)	6.8%	5 (0.3 ± 1.0)
Urge to defecate	11.4%	5 (0.4 ± 1.0)	9.1%	6 (0.5 ± 1.5)	6.8%	4 (0.2 ± 0.7)	6.8%	7 (0.3 ± 1.4)
Abdominal pain	0%	–	4.5%	2 (0.1 ± 0.5)	0%	–	0%	–
Loose stool/Diarrhea	0%	–	4.5%	4 (0.4 ± 1.5)	0%	–	4.6%	7 (0.4 ± 1.7)
Systemic								
Dizziness	9.1%	3 (0.1 ± 0.5)	13.6%	3 (0.2 ± 0.7)	2.3%	2 (0.1 ± 0.3)	6.8%	3 (0.2 ± 0.6)
Headache	36.4%	5 (0.6 ± 1.0)	18.2%	5 (0.3 ± 0.9)	9.1%	2 (0.1 ± 0.4)	18.2%	3 (0.2 ± 0.6)
Muscle cramps	2.3%	3 (0.1 ± 0.4)	2.3%	6 (0.1 ± 0.9)	2.3%	1 (0.0 ± 0.2)	0%	–
Urge to urinate	22.7%	8 (0.8 ± 1.9)	31.8%	8 (0.9 ± 1.7)	27.2%	7 (0.9 ± 1.7)	13.7%	5 (0.5 ± 1.2)

Percent incidence based on aggregate scores for each symptom reported at pre-, post-, 3 h post-, and 24 h post-exercise. Symptoms scored on a 0–9 scale.

GI distress

Fecal occult blood

There were no positive FOB tests pre-exercise. One positive FOB test indicated GI bleeding post-exercise in the Npx condition. However, this test was likely a false positive because it occurred in a menstruating participant.

GI symptoms pre-post exercise

Percent incidence and maximum and mean scores for individual GI symptoms were aggregated across time (pre-to 24 h post-exercise) and presented in Table 2. Compared to other time points, at 24 h post-exercise Heat experienced significantly more serious scores for reflux/heartburn, belching, bloating, stomach pain, nausea, intestinal cramps, flatulence, urge to defecate, loose stool/diarrhea, headache, and muscle cramps ($\chi^2(3) = 8.5$, $p = 0.037$).

Significant main effects occurred for aggregated upper ($\chi^2(3) = 7.8$, $p = 0.049$), lower ($\chi^2(3) = 10.9$, $p = 0.012$), and systemic ($\chi^2(3) = 8.4$, $p = 0.038$) GI symptoms at 3 h post-exercise between conditions. Post-hoc analysis indicated Control had higher mean scores, but this was not statistically significant. There were no other differences between conditions at any time point. Within conditions, there were significant main effects across time for upper symptoms in Control ($\chi^2(3) = 9.0$, $p = 0.029$) and systemic symptoms in Npx ($\chi^2(3) = 7.9$, $p = 0.048$); post-hoc analysis indicated post-exercise scores were higher than any other time, but these were not statistically significant. No differences occurred within Heat or NpxHeat.

GI symptoms during exercise

Percent incidence and maximum and mean scores for individual GI symptoms during exercise are presented in Table 3. NpxHeat reported less serious scores for urge to urinate compared to other conditions ($\chi^2(3) = 8.7$, $p = 0.033$). There were no other significant differences for individual symptoms or aggregated upper, lower or systemic symptom scores between conditions.

Correlations

We identified no significant correlations for GI symptoms to fluid volume, Tc, maximum RPE, or maximum HR within trials. During Heat, we found a significant positive correlation between lower and upper ($r_s = 0.9$, $p = 0.001$) and lower and systemic ($r_s = 0.7$, $p = 0.03$) GI symptoms. When examining correlations between non-GI measures, we found a significant positive correlation between maximum RPE and HR

Table 3
Mean and maximum gastrointestinal symptom scores for experimental conditions during exercise.

Symptoms	Control		Heat		Npx		NpxHeat	
	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)	Incidence	Max (M ± SD)
Upper								
Reflux/Heartburn	0%	–	0%	–	1.1%	2 (0.0 ± 0.2)	0%	–
Belching	0%	–	0%	–	0%	–	0%	–
Bloating	0%	–	4.5%	4 (0.1 ± 0.5)	3.4%	3 (0.1 ± 0.3)	1.1%	2 (0.0 ± 0.2)
Stomach pain	0%	–	4.5%	4 (0.1 ± 0.6)	5.7%	2 (0.1 ± 0.4)	0%	–
Vomiting	0%	–	1.1%	5 (0.1 ± 0.5)	0%	–	1.1%	7 (0.1 ± 0.7)
Nausea	4.5%	8 (0.2 ± 0.9)	2.3%	7 (0.1 ± 0.9)	1.1%	8 (0.1 ± 0.8)	1.1%	7 (0.1 ± 0.7)
Lower								
Intestinal cramps	13.6%	3 (0.3 ± 0.9)	4.5%	4 (0.1 ± 0.6)	0%	–	9.1%	3 (0.1 ± 0.4)
Flatulence	2.3%	1 (0.0 ± 0.1)	0%	–	0%	–	0%	–
Urge to defecate	0%	–	1.1%	4 (0.0 ± 0.4)	2.3%	4 (0.1 ± 0.4)	2.3%	4 (0.1 ± 0.6)
Abdominal pain	0%	–	0%	–	0%	–	0%	–
Loose stool/Diarrhea	0%	–	0%	–	0%	–	0%	–
Systemic								
Dizziness	3.4%	4 (0.1 ± 0.5)	1.1%	5 (0.1 ± 0.5)	0%	–	0%	–
Headache	9.1%	4 (0.2 ± 0.9)	1.1%	4 (0.0 ± 0.4)	0%	–	0%	–
Muscle cramps	0%	–	0%	–	0%	–	0%	–
Urge to urinate	20.4%	8 (0.8 ± 1.9)	10.2%	7 (0.4 ± 1.5)	26.1%	8 (0.9 ± 1.9)	5.6%	5 (0.1 ± 0.7)

for Control ($r_s = 0.8$, $p = 0.002$), Npx ($r_s = 0.8$, $p = 0.006$), and Heat ($r_s = 0.6$, $p = 0.043$), but not for NpxHeat. Distance travelled correlated significantly to maximum RPE during Npx ($r_s = 0.6$, $p = 0.044$) and to Tc during NpxHeat ($r_s = 0.7$, $p = 0.028$).

Discussion

We sought to determine whether a 24 h naproxen dose would negatively affect performance and induce GI symptoms during exercise in the heat. We chose this dose to identify acute effects from the over-the-counter strength medication using the recommended 1 pill every 8 h. Our results indicate, compared to placebo, an acute naproxen dose did not negatively impact RPE, distance, or maximum HR and did not significantly increase GI symptoms.

Performance

Contrary to our hypothesis, naproxen did not significantly decrease performance in either an ambient or thermal environment. Using a low naproxen dose is a potential explanation for the lack of statistical significance. Less COX-2 selectivity and shorter half-lives mean higher aspirin and ibuprofen doses are recommended to elicit anti-inflammatory and analgesic effects. Consequently, and compared to our naproxen dose, higher aspirin and ibuprofen doses are seen in the literature.[9–12] Increasing the naproxen dose (i.e., prescription strength) and extending time used (i.e., more than 24 h) could elicit different, more significant performance or GI responses. This concept is supported when examining acute versus chronic aspirin use, with acute only affecting RPE and chronic aspirin use negatively affecting RPE, lactate, hematocrit, and fatigue.[9]

Participants in the present study were euhydrated throughout exercise; therefore, increased HR was not dehydration induced but was associated with experimental conditions. The high correlation between maximum HR and maximum RPE in all conditions (except for NpxHeat) suggests participants were able to accurately assess their RPE and were exhibiting maximum effort at 90 min. Though not statistically significant, NpxHeat averaged fewer miles with higher HR and RPE compared to Heat. Slightly different results occurred among ambient conditions. Again, these were not statistically significant, but naproxen resulted in the greatest distance covered with no change in RPE and slightly higher HR. Keeping in mind NSAID effects on the cardiovascular system (vasoconstriction and increased blood pressure) and the cardiovascular system's response to intense exercise under thermal stress (increased HR to maintain cardiac output),[31] combining naproxen and heat could increase cardiovascular strain and maximum RPE, resulting in less distance. The potential environment influence when taking naproxen and exercising needs to be further elucidated.

Gastrointestinal distress

The etiology for GI distress is not well understood but is suggested to be attributed to mechanical vibrations,[32] GI ischemia-reperfusion,[33] and inflammatory responses.[33,34] Symptoms experienced in our study (i.e., nausea, diarrhea, vomiting) were similar to runners.[35] However, considering the prevalence of GI bleeding during running,[18] we were surprised to find a lack of positive FOB tests, particularly with the NpxHeat. We likely attenuated the incidence for GI bleeding by using a less impactful exercise (cycling) and a shorter, moderate-intense exercise bout.

Naproxen did not significantly increase GI distress compared to placebo. One interesting finding is that naproxen prevented dizziness and headache during exercise in both heat and ambient trials, but this effect was not observed before or after exercise. Though they were not significantly different, during Npx participants reported reflux/heartburn, bloating, and stomach pain, which were not reported during Control, and vomiting was only reported during heat trials. The only significant difference for individual GI symptoms between conditions occurred for urge to urinate, but in general was lower for both heat trails. Urination was likely mitigated by increased fluid needs in the hot environment due to sweating. Interestingly, higher incidence and serious scores were reported 24 h post-for Heat compared to ambient trials, and NpxHeat approached significance. These data suggest lingering effects from exercise in a hot environment, which was to some extent alleviated by naproxen. We did not assess physiological measures 24 h post-, but exercise and thermal stress induce inflammatory responses[24] that can last hours to days after.[36] Increased inflammation could explain higher GI symptoms 24 h post- and is an important consideration for individuals exercising on consecutive days, particularly in the heat.

In the present study, GI distress did not correlate with fluid volume consumed, Tc, maximum HR, or maximum RPE. Symptoms were most likely influenced by exercise, environment, and/or the presence of other GI symptoms. Performance variables seemed to be influenced more by one another, particularly between RPE and HR. Menstrual phase was not initially controlled for, but post-hoc analysis showed GI symptoms were not different for trials conducted during menstruation.

Limitations and future research

We assume participants were honest when answering the GI symptom indexes and that participants consumed the first 2 pills as instructed. We did not measure VO_{2max} or power output during exercise. Therefore, we must use HR and RPE to base our assumption that participants gave the same maximum effort each trial. Using a constant HR rather than VO_{2max} resulted in lower exercise intensity during heat trials because HR naturally increased in response to thermal strain. This forced participants to cycle at lower intensity to maintain target HR during the steady state. Less intensity may explain the lower percentage of incidence and serious GI symptoms in the heat. Frequency and severity for urge to urinate during and post-exercise were likely skewed by forcing participants to drink to maintain euhydration, making it difficult to determine actual naproxen effects. This limitation would be mitigated if participants drank the same fluid volume during each trial. Another potential limitation was using guaiac-based FOB, which has high specificity but low sensitivity, meaning it may not have been able to detect blood in the fecal samples, resulting in false negatives.

Future research should examine different NSAID dosages (e.g., prescription strength) and length of use (e.g., 3 days, 7 days). It is pertinent to examine effects in hypohydrated individuals, which would increase cardiovascular strain, GI distress, and perceived exertion in ambient and hot conditions. Using a carbohydrate electrolyte beverage for rehydration would introduce potential GI distress. Research is needed on different exercise modes, intensities, and durations and to identify potential differences between males and females.

Conclusion

Similar to previous studies using aspirin[9–11] and ibuprofen,[12] taking a 24 h over-the-counter naproxen dose did not improve or negatively affect performance. Our results are applicable to healthy, euhydrated, moderately trained individuals exercising at a given HR (e.g., as a way to maintain pace) prior to a maximum effort. An acute naproxen dose also did not cause GI bleeding or significantly increase upper, lower, or systemic GI symptoms during and after exercise. Bearing in mind NSAIDs' well-established effects on the cardiovascular and GI systems,[14,15,19,21,37] as well as our trend for higher HR with lower distance, consideration should be made for individuals taking naproxen before exercise in the heat, particularly if these individuals have predisposing factors that could compromise physiological function.

Authors' contributions

Conceptualization and Study Design: DME, JMD, SCLC, TMTM, CCE;

Data Acquisition: DME, TMTM, CEP, CCE, JDB, JVS; Data Analysis and Interpretation: DME, JMD, SCLC, TMTM; Drafting Manuscript: DME; Critical Revision of Manuscript: DME, JMD, SCLC, TMTM, CEP, CCE, JDB, JVS; Final Approval of Manuscript: DME, JMD, SCLC, TMTM, CEP, CCE, JDB, JVS.

Conflict of interest

Portions of this study were supported by funding from the American College of Sports Medicine Foundation and the National Athletic Trainers' Association Research and Education Foundation. The agencies had no role in the study design, data collection or analysis, or the writing and submitting for publication. The authors have no other conflict of interests to disclose.

Submission statement

This manuscript has not been published and is not under consideration for publication elsewhere.

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