Intestinal Permeability in Runners in the 1996 Chicago Marathon

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Abdominal cramping, nausea, diarrhea, and GI bleeding are often reported in long-distance runners. This study set out to determine the effects of prolonged (2–4 hrs) exercise and NSAID ingestion on gastric and intestinal permeability during the first 5 hrs following the 1996 Chicago Marathon. Thirty-four healthy volunteers (20 M, 14 F; ages 30–50) completed the race and ingested the test solution (5 g sucrose, 5 g lactulose, 2 g rhamnose, in 40 ml water) within 10–15 min. The urinary excretion ratio of lactulose/rhamnose was used to assess small intestine permeability; sucrose excretion was used to evaluate gastric impairment. There were no significant differences for mean training mileage, postrace rectal temperature, and percent dehydration between runners who ingested NSAIDs and those who did not. In all, 75% of subjects reported aspirin or ibuprofen ingestion before or during the race. Runners who ingested ibuprofen had significant elevations in urinary lactulose excretion and lactulose/rhamnose ratio, whereas those who ingested aspirin or who did not ingest either NSAID had no significant differences in urinary excretion of lactulose, rhamnose, sucrose, or lactulose/rhamnose ratio compared to resting controls. Thirteen of the 26 NSAID users and 4 of the 8 non-users reported GI symptoms. It is concluded that (a) ibuprofen but not aspirin ingestion during prolonged exercise may increase gastrointestinal permeability and lead to GI symptoms, and (b) prolonged exercise alone can produce GI symptoms.

Key Words: exercise, lactulose, rhamnose, stomach, small intestine

The gastrointestinal (GI) tract is not only important for the digestion and absorption of food and nutrients but also serves as an important barrier that restricts the movement of undesirable intraluminal pathogens into the interstitial fluid (7). This barrier includes epithelial cells, mucus, bacteria, and cells of the immune system, and blocks the penetration of androgenic, carcinogenic, or potentially toxic substances (4, 7). Barrier function is frequently assessed by its permeability, defined as the facility with which the intestinal epithelium allows molecules to pass by way of nonmediated diffusion (11). The breakdown of intestinal barrier function has
been demonstrated following strenuous exercise, ingestion of alcohol, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and thermal injury (17, 18). Recently we showed that running at 80% \( \text{VO}_2 \text{max} \) for 60 min significantly increased intestinal permeability (17), but few studies have focused on the effects of prolonged running, such as completing a marathon, on intestinal barrier integrity. GI symptoms such as cramps, diarrhea, bloating, nausea, and bleeding, commonly reported among long-distance runners, are believed to be caused in part by a breakdown of this barrier following prolonged exercise (3, 13). An increase in intestinal permeability due to the breakdown of barrier function, along with reduced blood flow to the gut, could contribute to GI distress during and after long-distance running.

Molecular permeation of the intestinal epithelium can occur via two pathways, transcellular and paracellular. Transcellular transport (through the cell) involves the movement of a substance from the apical cell membrane, through the cytoplasm and the basolateral membrane of the enterocyte. Paracellular transport (between cells) involves the movement of larger molecules (molecular mass >180 daltons) through the tight junctions between epithelial cells (9). These molecules subsequently enter the systemic circulation through the interstitial fluid between enterocytes. When tight junctions relax due to disease, exercise, alcohol, NSAID use, thermal injury, or high-intensity running, permeation of larger molecules is increased.

Alterations of intestinal barrier function can be quantitatively assessed using the urinary excretion of orally administered permeability probes (5, 10). Intestinal permeability tests have been shown to be useful in a variety of clinical situations. These tests have been recommended for use as diagnostic tools and for patient follow-up to identify potentially important alterations in intestinal barrier function (17, 18). Alterations in intestinal permeability, as measured by urinary excretion of orally administered sugars, have been documented in preterm neonates, patients with small intestinal villous atrophy, celiac disease, cystic fibrosis, acute and chronic diarrhea, food allergy, malnutrition, measles, human immunodeficiency virus (HIV), following ethyl alcohol ingestion (6), NSAID use, and high-intensity running (17). Suitable probes are nontoxic, water-soluble, metabolically inert, and quantitatively excreted in the urine.

A solution containing a disaccharide (lactulose) and a monosaccharide (rhamnose) is commonly used to evaluate small intestine permeability. The underlying assumption is that rhamnose, a smaller molecule, will permeate the epithelia transcellularly, while the larger lactulose molecule will pass paracellularly through the tight junctions between the epithelial cells (1, 17, 18). By expressing the percent urinary recovery of the ingested dose as a ratio of these two sugars, rhamnose can be used as a control for factors that are unrelated to intestinal permeability (gastric emptying, intestinal transit, renal excretion, etc.). An increase in the lactulose/rhamnose ratio is interpreted as an increase in small intestinal permeability.

A third carbohydrate contained in the permeability probe is sucrose, a disaccharide used to detect damage to the lining of the stomach and gastric permeability. Sucrose is broken down in the small intestine by the enzyme sucrase. Thus, alterations in its rate of urinary excretion reflect a change in permeability occurring in the stomach (14).

The purpose of this investigation was to explore the possible correlation between completing the Chicago marathon, ingestion of aspirin or ibuprofen, and the appearance and subjective severity of gastrointestinal symptoms.
Methods

Signed informed consent was obtained from 34 registered participants (20 men, 14 women) in the 1996 Chicago Marathon. Average age was 40 ± 11 years and average weight was 67 ± 10 kg. Average weekly training mileage prior to the marathon was 59.5 ± 14 km/wk. Participants consisted of four groups: (a) those who ingested aspirin before or during the marathon; (b) those who ingested ibuprofen before or during; (c) runners who did not ingest either substance; and (d) resting controls. Resting controls were trained runners (age 30 ± 2 yrs) participating in another study in our laboratory involving a strenuous running protocol. Their peak VO₂ max was 57.7 ± 2.1 ml · kg⁻¹ · min⁻¹.

One week prior to the marathon, each marathon study participant reported to the lab for prerace data collection. During this visit the subject was informed about the format of the study, and a nude weight, core temperature, and urine sample were obtained. Subjects also completed gastrointestinal and health-status questionnaires and provided their marathon history. The GI questionnaire was used to assess GI symptoms prior to the race. Subjects rated their perception of heartburn, nausea, cramping, defecation urge, and presence of a side-ache. The questionnaire consisted of a 100-mm horizontal line in which to rate the severity of GI symptoms. A mark at 0 mm indicated absence of the symptom; a mark at 100 mm indicated severe discomfort from the symptom. Presence of diarrhea and vomiting were assessed via other questions. The rest of the questionnaire requested information as to frequency and quantitative ingestion of alcohol, aspirin, ibuprofen, or caffeine before and during their regular physical activity. The purpose of the marathon history questionnaire was to assess current physical activity and running mileage as well as previous marathon experience. Subjects also filled out a health-status questionnaire listing general information about height, weight, current physician, and medications. They received a blank 3-day food and beverage log to report food and beverage ingestion for the 3 days prior to the marathon.

The day of the marathon, each subject reported to the experiment site within 15 min of completing the race. Subjects were immediately given a clinical rectal thermometer to assess core temperature, and a container to provide a urine sample. Each subject was then weighed and given another GI questionnaire concerning GI symptoms immediately after the race. Subjects were also given a food-and-drink-pattern questionnaire requesting information on the pattern of food and drink the day of the marathon, including food and beverages ingested before and during the race. They were instructed to follow their normal race-day pattern of food and drink and were asked to quantitatively report caffeine, alcohol, and aspirin/ibuprofen ingestion. Subjects were then seated and ingested a carbohydrate test solution consisting of 5 g sucrose, 5 g lactulose, and 2 g rhamnose in 40 ml of water. They were each given 3 liters of water and a urine collection container, and were instructed to collect urine for the 5 hrs immediately following ingestion of the test solution.

After the 5-hr urine collection period, subjects completed a final GI symptom questionnaire. Urine concentrations of sucrose, lactulose, and rhamnose were determined by high pressure liquid chromatography (Dionex DX-500). Urinary lactulose/rhamnose ratio, expressed as percent recovery of ingested dose, was used to assess small intestine permeability. The urinary excretion rate of sucrose, also expressed as recovery of ingested dose, was used to assess gastric permeability. Significant differences (p < 0.05) were evaluated via one-way ANOVA. Values are mean ± SE.
Results

There was no significant correlation between percent weight loss during the marathon and lactulose/rhamnose urinary excretion ratio. There were no significant differences in urinary excretion of rhamnose between runners who ingested aspirin or ibuprofen (13.3 ± 0.96% and 11.9 ± 1.0%, respectively), or in these two groups compared with runners who used neither substance (10.0 ± 1.4%) or resting laboratory controls (6.50 ± 1.4%) (Figure 1). There were no significant differences in urinary excretion of sucrose for aspirin users (1.04 ± 0.71%), ibuprofen users (1.51 ± 0.62%), or runners ingesting neither NSAID (0.364 ± 0.23%) vs. controls (0.301 ± 0.16%) (Figure 2). On the other hand, percent lactulose recovery was significantly increased in ibuprofen users (0.765 ± 0.14%) over non-aspirin users (0.218 ± 0.11%) and resting controls (0.280 ± 0.06%), but not in runners ingesting aspirin (0.674 ± 0.21%) or neither NSAID vs. resting controls (Figure 3). L/R ratio was not significantly elevated in aspirin users (0.048 ± 0.01) vs. non-aspirin users (0.019 ± 0.01) or resting controls (0.022 ± 0.01) (Figure 4). However, the L/R ratio for ibuprofen users (0.073 ± 0.015) was significantly increased over both the runners using neither NSAID and the resting control subjects. The correlation between NSAID use and L/R ratio was significant.

Results from the gastrointestinal questionnaires showed no correlation between aspirin or ibuprofen ingestion and the frequency or severity of GI symptoms. Half of the NSAID (either aspirin or ibuprofen) users reported some GI symptom

![Figure 1](image1.png)  
**Figure 1** — Five-hour urinary excretion of rhamnose expressed as percent recovery of ingested dose. Aspirin group (n = 6) reported ingestion of aspirin before or during the race. Ibuprofen group (n = 20) reported ingestion of ibuprofen before or during the race. Non-users (n = 8) reported no use of aspirin or ibuprofen before or during the race. Control group (n = 6) is resting control data from previous laboratory studies. No significant differences were found between groups.
Figure 2 — Five-hour urinary excretion of sucrose expressed as percent recovery of ingested dose. No significant differences were found between groups.

Figure 3 — Five-hour urinary excretion of lactulose expressed as percent recovery of ingested dose. Ibuprofen showed a significant increase in lactulose excretion over Non-users (*) and Control (†), p < 0.05.
occurrence, but there was no predictive relationship between NSAID use and physical complaint. Of the 8 runners who did not use either NSAID, 4 also reported physical complaints. Marathon history questionnaires showed no pattern between training mileage or marathon experience and GI symptoms or small intestine permeability. Diet history questionnaires were used for knowledge of caffeine and alcohol use patterns during the 3 days prior to the marathon. The goal of the questionnaires was to determine regular usage pattern of these substances to evaluate the possible correlation between use pattern and changes in intestinal permeability. There was no apparent relationship between alterations in small intestine permeability and pattern of caffeine and alcohol ingestion.

**Discussion**

Running at 80% VO$_{2}$max for 60 min has recently been shown to increase small intestine permeability (17). The current study investigated the effects of running duration, rather than exercise intensity, on intestinal and gastric barrier function. It also addressed the effect of ingestion of either aspirin or ibuprofen on changes in intestinal permeability which may be exacerbated when combined with endurance running. By assessing small intestine permeability in registered runners in the Chicago Marathon, we hoped to further explore the possible relationship between the gastrointestinal distress frequently reported in runners and alterations in the intestinal barrier function.

After completing the marathon, runners who ingested ibuprofen had a significant increase in intestinal permeability, as determined by an elevated lactulose/
rhamnose urinary excretion ratio. These subjects showed variable changes in su-
crose excretion, inconclusive of gastric damage. Although intestinal barrier func-
tion was compromised in these runners, the reported occurrence of GI symptoms
showed no correlation with changes in permeability. Oktedalen et al. (16) previ-
ously reported similar findings in marathon and half-marathon runners. The current
study reports no increases in intestinal permeability associated with aspirin inges-
tion during prolonged running, although we previously found that aspirin ingestion
significantly compromised GI barrier function during running at 60% VO2 max (18).
We suggest this is a result of the amount of aspirin ingested by the subjects. The
current marathon participants reported ingesting 400 to 800 milligrams before or
during the race, whereas the runners in our previous study were ingesting up to 2,600
milligrams within the 12-hr period preceding the running protocol.

Compromising the barrier integrity of the gut, whether due to high-intensity
running, thermal injury, or disease, has been proposed to allow the passage of
certain macromolecules across the intestinal epithelia. Passage of certain agents,
including bile and bacteria from the small intestine, may stimulate a local immune
response due to the recruitment of neutrophils to the area (5). This may lead to the
generation of free radicals and lysozomal enzymes, furthering epithelial damage. In
situations of heat stress or possible thermal injury, endotoxin has been shown to
enter the systemic circulation via passage across the gut epithelia, possibly leading
to the development of sepsis and multiorgan failure (2, 8, 15). This response has
been shown in humans due to severe burns, although its implications for exercise are
still unknown. It has long been known that the gut vasculature vasoconstricts during
exercise, to allow for the shunting of blood to active skeletal muscle (2). Baron et al.
(2) speculate that this decrease in blood flow may generate free radicals, again
possibly inducing a similar inflammatory response.

The different physiological actions of aspirin and ibuprofen may help explain
the different effects each has shown on the permeability of the small intestine in the
current study, although both substances have been reported to cause gastrointestinal
side effects. Sigthorsson et al. (19) have demonstrated less small intestinal inflam-
mation after aspirin ingestion when compared with other NSAIDs, including
ibuprofen. Aspirin is also one of the few NSAIDs that is not excreted in significant
amounts in the bile. It appears that the small intestinal mucosa may not be suffi-
ciently exposed to large enough quantities of aspirin to cause changes in permeabil-
ity. Most other conventional NSAIDs are associated with small intestine inflamma-
tory changes and gastrointestinal damage.

In summary, prolonged running, when combined with ibuprofen ingestion,
produced significant changes in small intestine permeability vs. runners who in-
gested no NSAIDs and vs. resting control subjects. There was no significant eleva-
tion in L/R ratio in aspirin users, indicating that aspirin ingestion combined with
running a marathon has no effect on intestinal permeability. This is in contrast to
other studies looking at the effect of aspirin on intestinal barrier integrity (1, 12, 18).
The occurrence of NSAID ingestion was not correlated with frequency or severity
of subjective sensations of GI distress. Sucrose permeability was variable and did
not conclusively indicate gastric damage. Further studies are needed to evaluate the
mechanism responsible for the alterations in small intestine permeability caused by
NSAID use and prolonged running. Additional examination is also needed to shed
light on the differences between the actions of aspirin and ibuprofen on intestinal
barrier function.
References


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