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Cimetidine Reduces Running-Associated Gastrointestinal Bleeding

A Prospective Observation

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A prospective observational study was undertaken to compare the effect of cimetidine usage immediately before and during a 100-mile running race on the frequency of detectable gastrointestinal bleeding and to relate these data to the frequency and intensity of gastrointestinal symptoms and to training data collected from pre- and postrace questionnaires. Nine of 25 runners in the 1989 Old Dominion 100-mile Endurance Race took 800 mg of cimetidine 1 hr before the start and at 50 miles. Sixteen other runners acted as controls and were not different in age, gender, or training data. All runners also submitted three stool specimens from the week before the race and from the first three bowel movements after the race on standard Hemoccult cards. All runners were Hemoccult negative before the race. One of the 9 (11%) cimetidine runners and 14 of the 16 (87.5%) control runners were Hemoccult positive afterwards ($P \leq 0.05$). Nausea and vomiting were less in those runners taking cimetidine ($P \leq 0.05$). There was no difference in the race performance as related to the ability to finish or in the number of miles run during the race. This study may help to define the etiology of this common gastrointestinal bleeding in these ultradistance runners and may be useful in preventing some of the symptoms associated with long-distance running.

KEY WORDS: running; gastrointestinal bleeding; cimetidine.

Gastrointestinal bleeding and troublesome digestive symptoms occur with endurance running events such as the marathon (1–11). The ultramarathon, which involves distances of 30–100 miles and lasts up to 24 hr, differs from the marathon in duration, pace, and dietary practices. A previous study demonstrated that ultramarathon runners complained of frequent and severe digestive distress, including frequent bowel movements, nausea and vomiting, bloating, and abdominal cramps. In addition, 85% of these runners developed occult bleeding (12); symptoms of profound hemorrhage were noted in some. During the past year some ultrarunners independently have begun to use cimetidine prophylactically with anecdotal success in reducing running-associated upper digestive distress and postrace melena. We performed a prospective observational trial to determine the incidence of digestive symptoms and occult gastrointestinal bleeding associated with a 100-mile ultramarathon in runners who either did or did not take cimetidine.

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MATERIALS AND METHODS

All 82 runners in the eleventh annual Old Dominion One Hundred Mile Endurance Run were contacted by mail and asked to participate. The race, held in June in mountainous western Virginia, must be completed in 24 hr, and is open only to experienced ultrarunners who qualify by completing a 50-mile race in 9 hr or less. The protocol was approved by the Human Use Committee of the Uniformed Services University of the Health Sciences and informed consent was obtained prior to enrollment.

Research participants completed a prerace questionnaire and returned three double-window Hemoccult cards (Smith Kline Diagnostics) collected during the week prior to the race. Following the race, a second questionnaire was completed and three more double-window Hemoccult cards from the first three bowel movements after the race were returned.

Data obtained from both a pre- and postrace questionnaire included demographics, running experience and training, dietary habits, medication usage, and digestive symptoms before and during the race. The questionnaire was designed with yes/no or single word answers and a graded value scale (0/none to 10/severe) for each of the following symptoms: heartburn, dark stools, indigestion, abdominal pain, abdominal cramping, nausea, vomiting, diarrhea, hematuria, and hematochezia.

All stool Hemoccult cards were developed within seven days of preparation as recommended by the manufacturer. The Hemoccult cards were developed without rehydration. A runner was considered to be Hemoccult positive if any of the three cards showed a positive change.

Runners were included as cimetidine users if they took 800-mg doses 1 hr before the start and at the 50-mile point of the race. While this medication was not dispensed by the researchers, the interval and dose was recommended to the runners. This schedule was based on the duration of histamine$_2$-receptor blockade effect and logistical access to the medication during the race. Runners taking antiulcer or antacid medication on a regular basis were excluded from the study.

Weight (by calibrated balance scale), blood pressure, and pulse were monitored every 20 miles as required by race rules. Although runners were to be disqualified from further race participation for a weight loss of >7%, no runner lost more than 5% of their starting weight.

Statistical analysis was performed utilizing the Statistix program with chi square and analysis of variance. Significance was established at the 0.05 level.

RESULTS

Of the 82 participants, 26 (30%) returned both questionnaires and the required stool Hemoccult specimens. One runner who missed the cimetidine dose at the 50-mile mark and converted to Hemoccult positive was disqualified from statistical analyses. Mean age (39.9 years), sex ratio (22 males and 4 females), previous 100-mile race experience (65%), and percent of finishers (46%) of the study group were similar to the overall race population. Nine of 25 (36%) runners took both cimetidine doses and were considered the treatment group. Sixteen (64%) did not use cimetidine and were considered the control group. There were no significant differences between the cimetidine and noncimetidine runners with regard to age, training history, prerace digestive symptoms, or finishing percentage. Control runners had more 100-mile race experience (12/16 vs 4/9, $P < 0.05$).

TABLE 1. POSTRACE HEMOCCULT RESULTS*

Group	*Positive*	*Negative*	*Totals*
Cimetidine	1 (11%)	8 (89%)	9
Control	14 (87.5%)	2 (12.5%)	16

*$P \leq 0.001$.

All prerace Hemoccult samples were negative. Following the race, 14/16 (87.5%) (Table 1) runners who did not use cimetidine converted to Hemoccult positive. Only one of the nine (11%) runners taking cimetidine converted to Hemoccult positive ($P < 0.05$).

Runners noted digestive symptoms commonly, but only nausea and vomiting were more frequent during the race ($P < 0.05$) in Hemoccult-positive runners. Cimetidine runners had less intense nausea scores (mean ± SD 1.3 ± 1.7 vs 4.3 ± 3.7) than those not taking cimetidine; no other digestive symptoms were group dependent. Training miles, percent of finishers, and medication usage including nonsteroidal antiinflammatory agents and aspirin were not associated with gastrointestinal bleeding (Table 2).

No runner was disqualified for weight loss of greater than 7% during the race, and there was no significant difference in weight change between the group that took cimetidine and those that did not.

TABLE 2. GENERAL CHARACTERISTICS OF SUBJECTS

	Cimetidine (N = 9)	*Control* (N = 16)
Age (years)	35.4 ± 8.4*	42.6 ± 6.4*
Gender	7M, 2F	14M, 2F
Miles/week	76.7 ± 21.5*	63.4 ± 18.9*
100-mile experience (%)	44.4	75.0
Finished this race (%)	44.4	43.8
Miles this race	85.4 ± 15.3*	85.7 ± 11.3*
Weight (lb)		
Prerace	152.5 ± 12.3*	150.6 ± 10.6*
Postrace	151.8 ± 9.8*	150.0 ± 12.5*

*Mean ± SD.

DISCUSSION

Gastrointestinal hemorrhage occurs in association with endurance running. Although gross bleeding, such as hematemesis, melena, or hematochezia, is not frequent, occult bleeding has been reported in 8–30% of marathon finishers and 85% of 100-mile ultramarathon runners (1–7, 12). This may contribute to selected cases of "runner's anemia" and, if sustained, to iron deficiency, events that may adversely affect recovery and performance of some competitive runners.

The site of running-associated intestinal bleeding is uncertain but bleeding lesions have been identified in the stomach and colon (13–18). By far the most frequently identified endoscopic abnormality has been hemorrhagic gastritis (14, 17). Generally it is described as fundic in location and appears to resemble the lesions seen in stress- or shock-associated gastritis. Although gastritis has been seen in runners who bleed, no data exist regarding the gastric mucosa of asymptomatic, nonbleeding marathon finishers.

The mechanism by which hemorrhagic gastritis develops in runners is also unknown, but it is usually attributed, in part, to ischemia. Running reduces visceral blood flow by up to 80% of preexercise levels (19, 20). No data exist regarding the blood flow of individuals who eat while running, but it is reasonable to assume a relative imbalance between supply and demand of bloodborne nutrients. Ultramarathon runners must drink and eat frequently to supply fluids and energy for their sustained activities. Thus, these runners would be expected to be more susceptible to ischemic-induced damage.

Another possible mechanism for the development of hemorrhagic gastritis is acid secretion. Experimental models of shock-induced hemorrhagic gastritis have demonstrated a requirement for luminal acid in the development of mucosal lesions (21, 22). Moderate-intensity running is generally not thought to affect gastric acid (23), whereas there is some evidence that heavy exertion acutely reduces acid secretion (24). Few data exist regarding meal-stimulated acid secretion during exercise or immediately following exercise. Thus, acid could still contribute to hemorrhagic gastritis of exercise. Some prior studies have implicated aspirin and nonsteroidal antiinflammatory agents (NSAIA) as causing hemorrhagic gastritis and gastrointestinal bleeding in runners (4, 25). We found no significant association between these medications and bleeding. Finally, hemorrhagic gastritis may result from direct mucosal trauma caused by shearing forces upon the gastric fundus from the diaphragm and the gastrophrenic ligaments. This possibility has not been evaluated.

Two prior reports have suggested that cimetidine might be useful in preventing running-associated gastrointestinal bleeding (14, 26). One case report clearly associated hemorrhagic gastritis with endurance running and found the condition to be reversible by either resting or running while taking therapeutic doses of cimetidine. We reasoned that if most cases of running-associated gastrointestinal bleeding were due to hemorrhagic gastritis, a medication such as cimetidine might prevent or ameliorate the bleeding.

During the 1988 Old Dominion, we noted a remarkably high incidence (85%) of Hemoccult-positive conversion after the race (8). Ultraendurance running is a unique sport. It differs from the marathon in distance, pace, duration, and intrarace ingestion of food and fluids. Runners during this race were offered various types of food and three types of electrolyte/glucose solutions approximately every five miles, and all runners reported that they drank and ate at most stations. In addition, most runners carried water bottles with them and some, additional food. Because of the length and terrain of this race in mountainous, rural Virginia, the pace is slower than a marathon. A portion of the race is run in darkness, also slowing the pace. Because of the slow pace, ultramarathoning places relatively low stress upon the musculoskeletal system and recovery time after such an event is short. Most competitors begin running again within several days. Anecdotal reports by the runners following the 1988 Old Dominion race were suggestive of symptomatic anemia and one runner noted a 6% decrease in hematocrit, a condition that disqualified him from volunteer plateletphoresis. Several of these runners began to use cimetidine prior to subsequent ultradistance running races and noted dramatic resolution in digestive complaints and gross evidence of bleeding, such as melena. Cimetidine has been approved for athletic use by the United States Olympic Committee during running events and over the past year its use has increased among this group of endurance athletes.

For the 1989 Old Dominion Race we performed a simple prospective observational trial to confirm the

results of the 1988 race and to determine whether cimetidine was effective in reducing the Hemoccult conversion. The noncimeditine runner's Hemoccult conversion rate was nearly identical to runners in last year's race (87.5% vs 85%). In contrast, the runners who used cimetidine had a marked reduction in Hemoccult conversion (11%). Although cimetidine may alter stimulated gastric mucosal blood flow, no data exist to suggest alterations in flow to other digestive organs (27). This implies that the majority of ultrarunning-associated gastrointestinal bleeding cases are likely secondary to hemorrhagic gastritis brought about by distance running.

This study may be criticized as being only observational since it was neither blinded nor randomized. Although both groups were comparable in terms of age, sex ratio, training history, race experience, and percent of finishers to the overall race participants, selection bias may have been introduced. However, the high percentage of Hemoccult conversion in the general race group makes this event ideal for evaluating the effectiveness of the medication. If the more symptomatic individuals had used cimetidine, it is likely that the difference observed would be even more impressive. Also, no attempt was made to document that the medication was taken as stated.

If cimetidine proves to have a role in treating the endurance runner, further studies will be required to determine which athletes are at greater risk for gastrointestinal bleeding. Although generally considered safe and well-tolerated, cimetidine has reported side effects such as cardiac conduction defects and alterations in mental status that could theoretically jeopardize runners who are voluntarily undergoing a somewhat hazardous activity (28, 29). To date, no adverse effects of cimetidine upon performance have been identified, but this area has been insufficiently investigated (30). A double-blinded, randomized trial evaluating its effectiveness and further experience and study of its safety in this group of athletes is clearly indicated before recommendations regarding general treatment can be offered.

In conclusion, these results strongly suggest that ultramarathon running-associated gastrointestinal bleeding is frequently caused by hemorrhagic gastritis and that cimetidine may be effective in decreasing symptoms and Hemoccult-positive bleeding, probably by decreasing the incidence or severity of gastritis.

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