

ORIGINAL ARTICLE

Proton pump inhibition prevents gastrointestinal bleeding in ultramarathon runners: a randomised, double blinded, placebo controlled study

M Thalmann, G H Sodeck, S Kavouras, A Matalas, K Skenderi, N Yannikouris, H Domanovits

Br J Sports Med 2006;**40**:359–362. doi: 10.1136/bjism.2005.024463

See end of article for authors' affiliations

Correspondence to: Dr Sodeck, Department of Emergency Medicine, Vienna General Hospital, Medical School, Waehringer Guertel 18–20, 6D Vienna A-1093, Austria; gottfried.sodeck@meduniwien.ac.at

Accepted 21 December 2005

Background: Ultra-endurance running is emerging as a popular sport in Western industrialised countries. Gastrointestinal bleeding has been reported to be an adverse effect in these runners.

Objective: To see if the oral administration of a proton pump inhibitor would reduce the incidence of gastrointestinal bleeding in an ultramarathon.

Methods: In a randomised, double blinded, placebo controlled study, a prophylactic regimen of three days of an oral proton pump inhibitor (pantoprazole 20 mg) was tested in healthy athletes participating in the Spartathlon ultramarathon. The incidence of gastrointestinal bleeding was assessed by a stool guaiac test.

Results: Results were obtained for 70 healthy volunteers. The data for 20 of 35 runners in the intervention group and 17 of 35 runners in the placebo group were entered into the final analysis. At the end of the ultramarathon, two subjects in the intervention group and 12 in the placebo group had positive stool guaiac tests (risk difference 0.86; 95% confidence interval 0.45 to 0.96; $p = 0.001$).

Conclusion: A short prophylactic regimen of oral proton pump inhibition can successfully decrease the incidence of gastrointestinal bleeding in participants in an ultramarathon.

Long distance running is emerging as a popular sport in Western industrialised countries.¹ Besides beneficial effects such as prevention of cardiovascular diseases, diabetes, and obesity, unintended adverse effects such as gastrointestinal symptoms, ranging from common diarrhoea to life threatening gastrointestinal bleeding, have been described.^{2–4} These symptoms may reflect the severe physical and psychological stress during long distance running and may affect athletic performance: abdominal pain at the wrong moment may make the difference between winning and losing. However, a specific treatment recommendation does not exist.^{4–8}

In the clinical setting, patients with gastrointestinal ulcer disease and bleeding have been successfully treated with histamine H₂ receptor antagonists for many years.⁹ Recently, however, proton pump inhibitors have shown superiority over histamine H₂ receptor antagonists in these indications.¹⁰ It has been shown that, in the particular setting of an ultramarathon, histamine H₂ receptor antagonists do not prevent the incidence of gastrointestinal bleeding.^{11 12} Proton pump inhibitors have not been yet evaluated in this setting. We speculated that a prophylactic regimen of an oral proton pump inhibitor would decrease the incidence of gastrointestinal symptoms, in particular bleeding, in healthy athletes participating in the Spartathlon ultramarathon. The hypothesis was tested in a randomised, double blinded, placebo controlled study.

METHODS

Study population

All healthy male and female competitors in the Spartathlon in Greece 2005 were eligible for this open, randomised, double blinded, placebo controlled study. The study was approved by the ethics committee of Harokopio University, Athens and performed according to the Declaration of Helsinki. Written informed consent was obtained from all

trial participants. Figure 1 gives the exact study time schedule.

Spartathlon participation criteria

The Spartathlon is one of the most gruelling running events in the world covering a distance of 246 km (from Athens to Sparta in Greece), which has been finished within 36 hours. Since the first International Spartathlon in 1983, runners from Australia, Japan, Canada, the United States, and Europe come every year, being attracted by the uniqueness and difficulty of the race.¹³ To compete, runners have to fulfil at least one of the following criteria: (a) must have finished a race of at least 100 km within 10 hours 30 minutes; (b) must have competed previously in the Spartathlon and reached a check point at 172 km in less than 24 hours 30 minutes; (c) must have reached the finishing point when competing in this ultramarathon regardless of the time; (d) must have competed in an event of more than 260 km and finished the race regardless of the time.

Exclusion and inclusion criteria

Participants had to fill in a questionnaire before randomisation to identify possible exclusion criteria: inability to comply with the study protocol; known allergy to pantoprazole or its excipients; current intake of any concomitant drugs; current known gastrointestinal bleeding over a six month period before the race; self reported history of anal fissures or haemorrhoids and general haematological disorders such as anaemia, clotting dysfunction, or hypercoagulability.

Randomisation and data analysis

After written informed consent and negative guaiac stool results had been obtained, participating athletes were assigned to the placebo or intervention group using permuted randomisation blocks of five from a computer generated randomisation list.

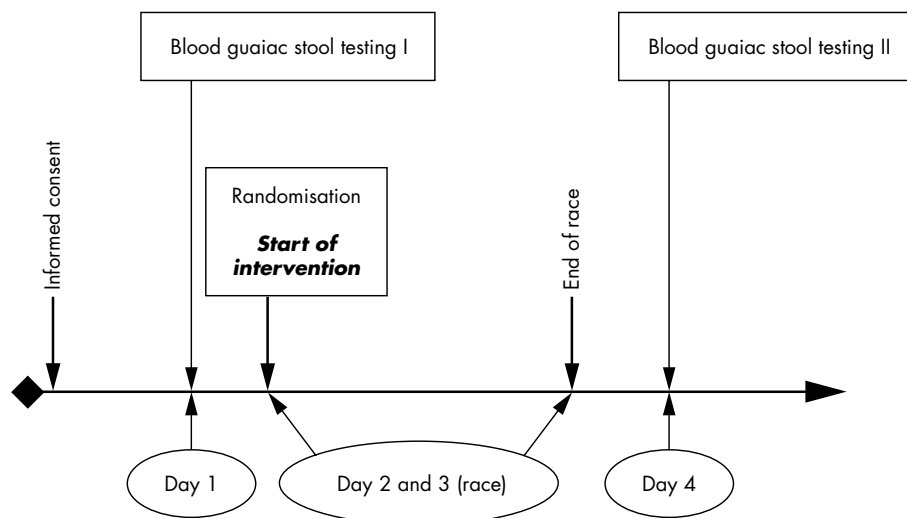


Figure 1 Time schedule of study. After written informed consent and negative stool guaiac tests had been obtained, participants were randomised to receive either pantoprazole or placebo for three days. Assessment of efficacy was performed after the ultramarathon.

For logistic reasons and for homogeneity of stress exposure, the athletes had to finish the race within 36 hours for their data to be used in the final analysis. The final analysis was performed as a per protocol analysis. Continuous data are presented as the median and interquartile range (25th to 75th centile). Discrete data are given as counts and percentages. A two sided p value below 0.05 was considered significant. Calculations were performed with SPSS for Windows (version 10.0).

Stool guaiac test

Stool guaiac test kits for occult gastrointestinal bleeding (Haemdetect) were from BeckhamCoulter Inc, Tuttlingen, Germany. According to the manufacturer's instructions and the study protocol, athletes placed three different representative stool specimens on the diagnostic site of the test kits before and after the Spartathlon, in order to obtain reliable results. Analysis was performed by researchers blinded to the study protocol. In accordance with the manufacturer, a distinct blue zone at the diagnostic site in three consecutive examinations was considered to be a positive result.

Study drug

Pantoprazole disodium tablets (Pantoloc 20 mg) and placebo tablets of the same size, shape, and colour were provided by Altana Pharmaceutical Ltd, Vienna, Austria. Neither the study participants nor the recruiting centre could distinguish between the proton pump inhibitor and placebo tablets. All participants were instructed to swallow the tablets without chewing in the early morning with a glass of natural water. Enough tablets for three days were handed over to the participants in coded envelopes with detailed instructions. The randomisation centre was blinded to the code applied.

Table 1 Basic characteristics of study group and eligible group

	Study group (n = 70)	Eligible group (n = 232)
Age (years)	42 (37–51)	47 (39–52)
Male sex	65 (93%)	209 (90%)
Drop outs	33 (47%)	125 (54%)

Values in parentheses are interquartile range or percentage.

RESULTS

In total, 232 Spartathlon competitors were eligible for participation in the study. There was no significant difference between the whole group of participants and the finally included study cohort and eligible group (table 1). After written informed consent and a negative stool guaiac test had been obtained, 70 athletes were randomised. Table 2 gives some of their characteristics, and fig 2 is the study flow chart. Three subjects (two in the placebo group, one in the intervention group) dropped out of the study after randomisation. In four athletes, a history of gastritis or gastric ulcer disease was found. Furthermore, current tobacco smoking, which is considered to be a major risk factor in the development of gastric mucosal bleeding, was evident in the same four runners. Two were in the intervention group and two in the placebo group.

Thirty seven study participants finished the race at the defined check point for further study participation and examination according to the study protocol: 20 of 34 runners in the intervention group, 17 of 33 runners in the placebo group. Two male athletes in the intervention group and 12 participants (all of them male) in the placebo group had a positive stool guaiac test (risk difference 0.86; 95% confidence interval 0.45 to 0.96; $p = 0.001$). None of the participants with a positive test needed to be admitted to hospital, thus the bleeding must be considered a minor event.

DISCUSSION

This is the first study to show that a prophylactic regimen of oral proton pump inhibition can result in a significant reduction in the incidence of gastrointestinal bleeding in healthy volunteers during severe extended sporting activity.

Table 2 Basic characteristics of intervention group and placebo group

	Intervention group (n = 35)	Placebo group (n = 35)
Age	40 (35–47)	44 (36–49)
Male sex	33 (94%)	32 (91%)
Drop outs	15 (43%)	18 (51%)
History of gastritis	2 (6%)	2 (6%)
Smokers	2 (6%)	2 (6%)

Values in parentheses are interquartile range or percentage.

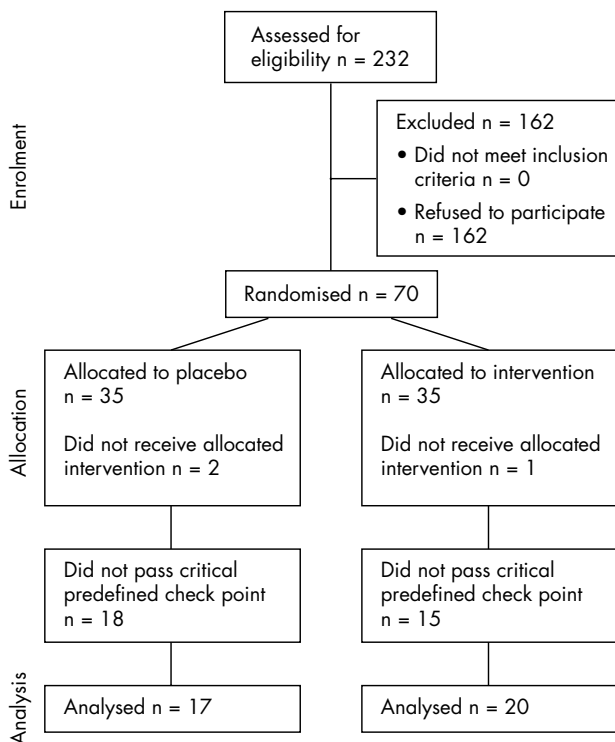


Figure 2 CONSORT diagram showing the flow of participants through each stage of the study.

The healthy volunteers who received 20 mg pantoprazole orally for three days were less likely to have a positive stool guaiac test after competing in an ultramarathon race. None of the participants reported any adverse effects of the treatment.

Previous investigations of the beneficial effects of histamine H₂ receptor antagonists^{11, 12} in the prevention of stress related mucosal disease during long distance running showed no improvement in the incidence of gastrointestinal bleeding. Prospective randomisation was performed in only one study.¹² In both these studies, the assessment of efficacy was based on stool guaiac testing, as in our study.

However, in daily clinical practice, endoscopy is the optimum method of assessing gastrointestinal bleeding, providing the exact localisation and description of the extent.^{11, 12} The stool guaiac test is a well established screening tool.^{14–16} In our study setting of healthy volunteers under severe physical and emotional stress, repeated endoscopy would not be acceptable; therefore the stool guaiac test is a more feasible and reasonable method.

Although bleeding lesions anywhere in the gastrointestinal tract may cause a positive reaction in guaiac based faecal occult blood tests, upper gastrointestinal lesions are identified more often than colonic lesions.^{14–16} There are two reports on marathon runners with a positive stool guaiac test; endoscopic examination revealed 90–100% upper gastrointestinal bleeding lesions.^{17, 18} However, we cannot definitely exclude the possibility that athletes from our cohort had minor upper gastrointestinal bleeding which may have not been detected by the test.

Clinically important or life threatening bleeding in long distance runners occurs only rarely, but diffuse superficial erosions of the gastric mucosa, which are signs of stress related injury, are commonly observed.^{19–22} The extent of exercise related gastrointestinal symptoms correlates with the occurrence of such symptoms during non-exercise periods and depends on age, sex, diet, and years of training.²⁰

What is already known on this topic

- Gastrointestinal disturbances are common in runners
- Serious bleeding is rare, but minor bleeding is common and related to gastrointestinal bleeding during non-exercise periods, higher age, female sex, diet, and years of training.

What this study adds

- In athletes with increased risk of gastrointestinal bleeding, the use of prophylactic proton pump inhibition may be reasonable during heavy and/or prolonged sports activity

In line with previous reports, in our study both subjects in the placebo group with a history of gastrointestinal bleeding had a positive stool guaiac test after the race. In the intervention group, however, none of the athletes at high risk had a positive stool guaiac test. We speculate that this finding indicates that prophylactic proton pump inhibition may be effective for athletes with increased risk of gastrointestinal bleeding during heavy and/or prolonged sports activity.

We found the risk difference for bleeding to be 0.86 within a small 95% confidence interval of 0.45 to 0.96. These findings are based on a per protocol analysis of 37 out of 232 runners. Most of the runners (162) refused to participate in this medical study because of lack of interest, anxiety, and language problems. However, the criteria for entering the final analysis created a nearly “ideal” study population. Nevertheless, our results, even though statistically significant, ideally need confirmation in different, larger cohorts.

Although intention to treat analysis is considered to be optimum in randomised controlled trials, our final analysis was performed per protocol because of the limitations of the study design.

Conclusion

A three day prophylactic regimen of oral pantoprazole may decrease the incidence of gastrointestinal bleeding in ultramarathon runners.

Clinical implications

Medical practitioners should be aware that gastrointestinal disturbances are common among runners. Serious bleeding is rare, but minor bleeding is common and correlates with gastrointestinal bleeding during non-exercise periods, higher age, female sex, diet, and years of training. On the basis of our results, in these groups with increased risk of gastrointestinal bleeding, the use of prophylactic proton pump inhibition may be reasonable during heavy and/or prolonged sports activity. However, it cannot be recommended for every athlete.

.....
Authors’ affiliations

M Thalmann, Department of Cardiothoracic Surgery, Lainz- Hospital, Vienna, Austria

G H Sodeck, H Domanovits, Department of Emergency Medicine, Vienna General Hospital, Medical School, Vienna

S Kavouras, A Matalas, K Skenderi, N Yannikouris, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

Competing interests: none declared

M Thalmann and GH Sodeck contributed equally to this work.

REFERENCES

- 1 **Thompson PD**, Buchner D, Pina IL, *et al*. American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Rehabilitation, and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism Subcommittee on Physical Activity. *Circulation* 2003;**107**:3109–16.
- 2 **Moses FM**. Gastrointestinal bleeding and the athlete. *Am J Gastroenterol* 1993;**88**:1157–9.
- 3 **Halvorsen FA**, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol* 1986;**21**:493–7.
- 4 **Bounous G**, McArdle AH. Marathon runners: the intestinal handicap. *Med Hypotheses* 1990;**33**:261–4.
- 5 **Oktedalen O**, Lunde OC, Opstad PK, *et al*. Changes in the gastrointestinal mucosa after long-distance running. *Scand J Gastroenterol* 1992;**27**:270–4.
- 6 **Rudzki SJ**, Hazard H, Collinson D. Gastrointestinal blood loss in triathletes: its aetiology and relationship to sports anaemia. *Aust J Sci Med Sport* 1995;**27**:3–8.
- 7 **Peters HP**, Bos M, Seebregts L, *et al*. Gastrointestinal symptoms in long-distance runners, cyclists, and triathletes: prevalence, medication, and etiology. *Am J Gastroenterol* 1999;**94**:1570–81.
- 8 **Dimeo FC**, Peters J, Guderian H. Abdominal pain in long distance runners: case report and analysis of the literature. *Br J Sports Med* 2004;**38**:E24.
- 9 **Cook D**, Guyatt G, Marshall J, *et al*. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998;**338**:791–7.
- 10 **Leontiadis GI**, McIntyre L, Sharma VK, *et al*. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2004;(3):CD002094.
- 11 **Cooper BT**, Douglas SA, Firth LA, *et al*. Erosive gastritis and gastrointestinal bleeding in a female runner. Prevention of the bleeding and healing of the gastritis with H2-receptor antagonists. *Gastroenterology* 1987;**92**:2019–23.
- 12 **Moses FM**, Baska RS, Peura DA, *et al*. Effect of cimetidine on marathon-associated gastrointestinal symptoms and bleeding. *Dig Dis Sci* 1991;**36**:1390–4.
- 13 <http://www.spartathlon.org> (accessed 15 Oct 2005).
- 14 **Rockey DC**, Auslander A, Greenberg PD. Detection of upper gastrointestinal blood with fecal occult blood tests. *Am J Gastroenterol* 1999;**94**:344–50.
- 15 **Harewood GC**, McConnell JP, Harrington JJ, *et al*. Detection of occult upper gastrointestinal tract bleeding: performance differences in fecal occult blood tests. *Mayo Clin Proc* 2002;**77**:23–8.
- 16 **Rockey DC**, Koch J, Cello JP, *et al*. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. *N Engl J Med* 1998;**339**:153–9.
- 17 **Schwartz AE**, Vanagunas A, Kamel PL. Endoscopy to evaluate gastrointestinal bleeding in marathon runners. *Ann Intern Med* 1990;**113**:632–3.
- 18 **Choi SC**, Choi SJ, Kim JA, *et al*. The role of gastrointestinal endoscopy in long-distance runners with gastrointestinal symptoms. *Eur J Gastroenterol Hepatol* 2001;**13**:1089–94.
- 19 **McCabe ME 3rd**, Peura DA, Kadakia SC, *et al*. Gastrointestinal blood loss associated with running a marathon. *Dig Dis Sci* 1986;**31**:1229–32.
- 20 **Riddoch C**, Trinick T. Gastrointestinal disturbances in marathon runners. *Br J Sports Med* 1988;**22**:71–4.
- 21 **Fisher RL**, McMahon LF Jr, Ryan MJ, *et al*. Gastrointestinal bleeding in competitive runners. *Dig Dis Sci* 1986;**31**:1226–8.
- 22 **Stewart JG**, Ahlquist DA, McGill DB, *et al*. Gastrointestinal blood loss and anemia in runners. *Ann Intern Med* 1984;**100**:843–5.

COMMENTARY

The issue of gastrointestinal bleeding in endurance runners is a well know clinical entity. The causes are multifactorial. The dilemma is that the extent of bleeding is often minor, one could say almost physiological, and therefore does it warrant treatment? The study has been well designed and the limitations recognised. The potential benefit of a prophylactic proton pump inhibitor in those with gastrointestinal

disturbances would be primarily to enhance performance and modify symptom presentation. On the whole this has been well illustrated. Clearly the next step would be to scientifically validate an increase in performance time with the drug's usage, although I concede that indirect criteria have been used in this study. The other issue pertains to associated symptoms. It is very rare that athletes with gastrointestinal disturbances present with isolated gastrointestinal bleeding. Often there is associated abdominal distension, vomiting, diarrhoea, etc. This has been alluded to in the study. It is therefore important to show whether the effects of the drug are specific to gastrointestinal bleeding or not.

A Rao

Specialist Sportscore, Marylands, WA, Australia;
a.rao@bigpond.net.au

COMMENTARY

Gastrointestinal bleeding is a well known consequence of intense and long duration running and other endurance events. Upper and lower gastrointestinal sources are implicated. There is probably little clinical implication for this small quantity blood loss. However, repetitive small quantity blood loss may contribute to anaemia and subsequent performance decline. The authors determine a protective benefit from prophylactic proton pump inhibitor in this cohort from an extreme endurance event. Extrapolation to the more common shorter and less intense events remains speculative. Nonetheless the results of this study support consideration of the prophylactic use of proton pump inhibitors by ultradistance athletes.

S Simons

Sports Medicine Institute, Saint Joseph Regional Medical Center,
Mishawaka, IN, USA; simonss@sjrhc.com

COMMENTARY

This paper shows that administration of proton pump inhibitors significantly reduces the incidence of exercise induced gastrointestinal bleeding. The effect of physical exercise on the gastrointestinal tract is still unclear. This work sends an important message to medical practitioners, in particular those who see athletes with gastrointestinal symptoms.

E Yazaki

Barts and The London School of Medicine and Dentistry, London, UK;
e.yazaki@qmul.ac.uk