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Papers

Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: the prevention of high altitude illness trial (PHAIT)

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Abstract

Objective To evaluate the efficacy of ginkgo biloba, acetazolamide, and their combination as prophylaxis against acute mountain sickness.

Design Prospective, double blind, randomised, placebo controlled trial.

Setting Approach to Mount Everest base camp in the Nepal Himalayas at 4280 m or 4358 m and study end point at 4928 m during October and November 2002.

Participants 614 healthy western trekkers (487 completed the trial) assigned to receive ginkgo, acetazolamide, combined acetazolamide and ginkgo, or placebo, initially taking at least three or four doses before continued ascent.

Main outcome measures Incidence measured by Lake Louise acute mountain sickness score ≥ 3 with headache and one other symptom. Secondary outcome measures included blood oxygen content, severity of syndrome (Lake Louise scores ≥ 5), incidence of headache, and severity of headache.

Results Ginkgo was not significantly different from placebo for any outcome; however participants in the acetazolamide group showed significant levels of protection. The incidence of acute mountain sickness was 34% for placebo, 12% for acetazolamide (odds ratio 3.76, 95% confidence interval 1.91 to 7.39, number needed to treat 4), 35% for ginkgo (0.95, 0.56 to 1.62), and 14% for combined ginkgo and acetazolamide (3.04, 1.62 to 5.69). The proportion of patients with increased severity of acute mountain sickness was 18% for placebo, 3% for acetazoalmide (6.46, 2.15 to 19.40, number needed to treat 7), 18% for ginkgo (1, 0.52 to 1.90), and 7% for combined ginkgo and acetazolamide (2.95, 1.30 to 6.70).

Conclusions When compared with placebo, ginkgo is not effective at preventing acute mountain sickness. Acetazolamide 250 mg twice daily afforded robust protection against symptoms of acute mountain sickness.

Introduction

Acute mountain sickness is a syndrome that occurs above 2000 m secondary to failed physiological adaptation to acute hypobaric hypoxia. This rapidly reversible condition is characterised by headache, lightheadedness, fatigue, nausea, and insomnia. If untreated the condition may progress to life threatening high altitude cerebral oedema or pulmonary oedema.[1 2] Although modifiable aspects of high altitude travel such as ascent rate and exertion are the primary mediators of risk, pharmaceutical prevention with acetazolamide is also effective despite common side effects such as parasthesias, dysgeusia, and diuresis, which may reduce compliance. Acute mountain sickness is a common diagnosis at high altitude, and effective, readily available, and safer prophylactic agents are needed.

Ginkgo biloba is a popular herbal supplement, which has emerged as a new prophylactic agent for the prevention of acute mountain sickness.[3–8] Indirect evidence suggests that it may prevent hypoxic damage in tissues in part as a result of its antioxidant activity, and in clinical trials its side effects profile was similar to placebo.[9 10] Our group has shown that prophylactic ginkgo may lead to a reduction in acute mountain sickness, with no recognisable side effects, indicating that it may be a viable alternative to acetazolamide.[4] The results of multiple small randomised controlled trials with ginkgo have, however, been mixed.

To date there have been no large scale, randomised controlled trials comparing ginkgo with acetazolamide on prevention of acute mountain sickness or testing the two combined for safety and additive efficacy. We compared the effect either ginkgo, acetazolamide, or combined ginkgo and acetazolamide with placebo on the incidence and severity of acute mountain sickness and headache in people who trek at high altitudes.

Methods

Our study was designed as a prospective, randomised, double blind, placebo controlled trial. Enrolment took place between 6 October and 24 November 2002 along the Mount Everest approach in the Nepal Himalayas.

The predetermined primary outcome measure was incidence and severity of acute mountain sickness at the study end point as judged by the Lake Louise scoring system, a well validated standard for evaluation of acute mountain sickness in the field.[11–13] Acute mountain sickness is quantified on the Lake Louise questionnaire in a high altitude setting as a score of three or greater, with headache and at least one of the symptoms of nausea or vomiting, fatigue, dizziness, or difficulty sleeping. Predetermined secondary end points included incidence and severity of headache and endpoint pulse oximetry (Nonin Medical Products, Minneapolis, USA). Personal data, ascent profile, com-

pliance, and side effects were analysed to discount potential confounders.

Our trial was double blinded, and the randomisation code was computer generated by Deurali-Janta Pharmaceuticals (Kathmandu, Nepal) and held by an independent physician. The standardised ginkgo extract GK 501 was manufactured by Pharmaton (Lugano, Switzerland) in strict accordance with German European Commission standards, with no less than 24% ginkgoflavone glycosides and 6% terpenes. The acetazolamide was manufactured by Wyeth (Madison, USA). Samples from the randomised batch of study drugs were verified for purity and activity by Boehringer-Ingelheim (Germany).

Randomisation and follow up

Trekkers completed questionnaires after giving signed informed consent. Inclusion criteria specified healthy non-Nepali males and females aged 18-65 years travelling directly between the baseline villages of Pheriche or Dingboche (4280 m and 4358 m, respectively) and the end point in Lobuje (4928 m). Potential participants were excluded if they had acute mountain sickness, had signs and symptoms of a substantial acute infection, had slept above 4500 m, had taken ginkgo or acetazolamide within two weeks before enrolment, or had any known cardiac, pulmonary, or other chronic disease that would render them at increased risk of altitude illness.

Trekkers newly arrived at the baseline altitude were screened daily and serially enrolled by randomisation number. They completed the Lake Louise questionnaire, had pulse oximetry readings taken, and provided data on personal characteristics and rate of ascent. They were given information on methods for reducing the risk of acute mountain sickness. Participants were randomised in a double blind fashion to receive twice daily either ginkgo 120 mg, acetazolamide 250 mg, combined ginkgo 120 mg and acetazolamide 250 mg, or placebo. Participants took a minimum of three or four doses of the study drugs at baseline altitude before proceeding on their trek without any influence from study administrators. On their ascent from baseline, some participants stopped overnight at a lodge at 4595 m, but all were expected to arrive at the end point altitude for data collection (Lake Louise questionnaire, pulse oximetry, rate of ascent, and side effects). Lake Louise scores were taken the morning after arrival, after which the study was complete.

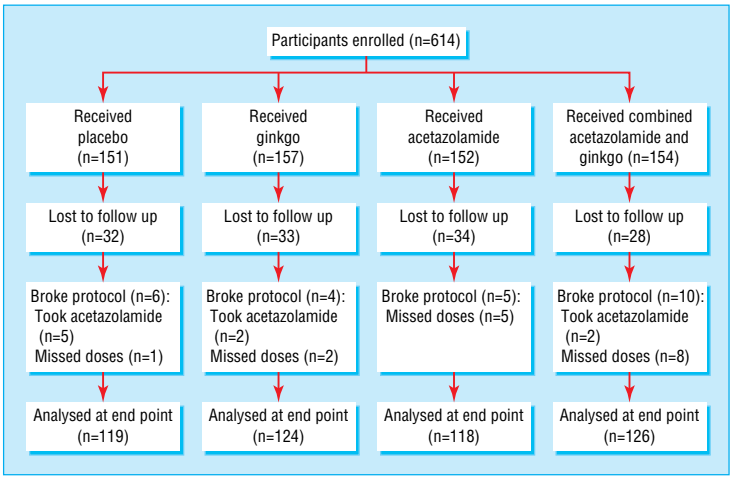
Power calculation and statistical analysis

Preliminary estimates suggested that we would need a minimum sample size of 70 people per group to determine a statistically significant difference (80% power) between treatment and placebo groups based on a published acute mountain sickness attack rate of 57% at the end point.[14] We used odds ratios and associated confidence intervals (asymptotic or Fisher's exact test) to estimate the effects of categorical variables (confidence intervals excluding one represent significant effects). Means of continuous outcomes were compared using *t* tests, and we considered P values less than 0.05 as significant.

Results

Overall, 614 trekkers were enrolled and 487 completed the study (figure). Participants in all four groups, including those lost to follow up, were similar at baseline (table 1). The 127 participants (20.7%) lost to follow up had similar personal characteristics to all participants (data not shown).

Table 2 summarises the main outcome profile for the 487 participants who completed the study. The data are presented as an intention to treat analysis; there were no significant changes noted when the table was reproduced without the data from non-compliant participants (data not shown). Analysis for the primary end point showed that ginkgo did not reduce the incidence of acute mountain sickness when compared with placebo; ginkgo also failed to show a benefit in secondary analyses. The small increase in incidence and severity of acute mountain sickness or headache in the ginkgo group was not significant when compared with placebo. We found no significant adverse events in any group (aggressive allergic reactions or high altitude cerebral oedema or pulmonary oedema).



Flow of participants through trial

Acetazolamide as a control intervention was associated with a substantial decrease in acute mountain sickness and incidence and severity of headache, as well as improved blood oxygen desaturation with ascent when compared with placebo. In the acetazolamide group the numbers needed to treat were 4 to prevent one instance of acute mountain sickness, 7 to prevent one instance of severe acute mountain sickness, 3 to prevent one instance of headache, and 8 to prevent headaches of greater severity. When compared with acetazolamide the combined drug caused a marginally significant increase in the incidence of headache (odds ratio 1.82, 95% confidence interval 1.0 to 3.3, number needed to harm 9) but did not significantly affect other surrogate markers (incidence of acute mountain sickness 1.24, 0.6 to 2.6; severity of acute mountain sickness 2.19, 0.7 to 7.3; severity of headache 1.90, 0.3 to 10.6).

The groups were compared for inequality in several measures, but we found no bias or inequality at the end point excepting the typical side effects of acetazolamide (table 3).

Discussion

Ginkgo was not effective in reducing the incidence or severity of acute mountain sickness when compared with placebo and failed to show a protective benefit for any outcome measure. Furthermore, the addition of ginkgo to acetazolamide caused a marginally significant decrease in the efficacy of acetazolamide against headache (the most common symptom at altitude); this was unexpected considering the different proposed mechanisms of action for the two substances. Research has shown ginkgo to have some vasodilatory properties.[15] This may theoretically increase cerebral blood flow, which in turn could worsen the symptoms of acute mountain sickness such as headache. Regardless of the mechanism, clinicians should avoid recommending ginkgo as prophylaxis for acute mountain sickness either alone or combined with acetazolamide.

Table 1 Baseline characteristics of 487 of 614 participants who completed study on effects of prophylactic agents against acute mountain sickness

Variables	All participants (n=487)	Study groups			
		Placebo (n=119)	Acetazolamide group (n=118)	Ginkgo group (n=124)	Combined acetazolamide and ginkgo (n=126)
No (%) male	337 (69)	88 (74)	79 (67)	83 (67)	88 (70)
Mean (SD) age (years)	36.6 (10.9)	36.4 (10.8)	36.4 (11.0)	36.7 (10.5)	36.7 (11.4)
No (%) if trekkers starting from 2800 m*	395 (81)	91 (76)	101 (86)	104 (84)	99 (79)
Mean No (SD) nights to ascend from 2800 m	4.7 (1.3)	4.6 (1.2)	4.7 (1.1)	4.5 (1.9)	4.9 (1.5)
No (%) enrolled at 4358 m†	259 (53)	67 (56)	58 (49)	68 (55)	66 (52)
No (%) with baseline Lake Louise score of 1‡	27 (5)	6 (5)	7 (6)	6 (5)	8 (6)
Mean (SD) baseline oxygen saturation	85.4 (4.3)	85.9 (4.3)	85.3 (4.4)	84.8 (4.8)	85.5 (3.7)
No (%) lost to follow up§	127 (26)	32 (27)	34 (29)	33 (27)	28 (22)

*Lukla airport is at about 2800 m, and trekkers starting from Jiri (2000 m) pass through Lukla.
†Enrolment occurred in villages of Dingboche (4358 m) and Pheriche (4280 m).
‡Most participants at baseline scored zero.
§From original 614 participants.

This is the first study in which ginkgo prophylaxis was given when the participants were enrolled at a high baseline altitude (as opposed to starting the drug at sea level before ascent). This may explain why our results were negative compared with previous trials. Other reasons include the quality and purity of the ginkgo preparations, the dose of ginkgo used, the number of days in which ginkgo was preloaded before controlled ascent, and environmental or behavioural influences on ginkgo's effectiveness.

Our study is among the largest randomised trials of acetazolamide for acute mountain sickness prophylaxis, and the 250 mg twice daily regimen exhibited a robust and predictable

Table 2 Main outcome profile (intent to treat) in groups treated with prophylactic agents for acute mountain sickness. Values are numbers (percentages) unless stated otherwise

Variables	All participants (n=487)	Placebo group (n=119)	Acetazolamide group (n=118)	Odds ratio (95% CI)*	Ginkgo group (n=124)	Odds ratio (95% CI)*	Combined acetazolamide and ginkgo group (n=126)	Odds ratio (95% CI)*
Incidence of acute mountain sickness†	115 (24)	40 (34)	14 (12)	3.76 (1.91 to 7.39)	43 (35)	0.95 (0.56 to 1.62)	18 (14)	3.04 (1.62 to 5.69)
Severe acute mountain sickness‡	58 (12)	22 (18)	4 (3)	6.46 (2.15 to 19.40)	23 (18)	1.00 (0.52 to 1.90)	9 (7)	2.95 (1.30 to 6.70)
Headache incidence	197 (40)	63 (53)	23 (19)	4.77 (2.70 to 8.44)	72 (58)	0.75 (0.47 to 1.22)	39 (31)	2.62 (1.58 to 4.35)
Severe headache§	46 (9)	16 (13)	2 (2)	9.01 (2.02 to 40.13)	24 (19)	0.65 (0.32 to 1.29)	4 (3)	4.74 (1.54 to 14.62)
Mean endpoint oxygen saturation (%)¶	82.3	82.1	83.7	P=0.01	79.5	P<0.01	83.9	P<0.01
Decrease in oxygen saturation from baseline¶	3.0	3.8	1.7	P<0.01	5.2	P=0.04	1.5	P<0.01
Non-compliant**	25 (5)	6 (5)	5 (4)	0.75 (0.75 to 2.10)	4 (3)	1.49 (0.46 to 4.76)	10 (8)	0.59 (0.22 to 1.56)

*Compared with incidence in placebo group.
†Lake Louise score ≥3 with headache and at least one other symptom.
‡Lake Louise score ≥5.
§Determined by cut off between scores of 1 and 2 on the Lake Louise survey (ascending scale of 0-3 for severity).
¶Mean values reported, with P values of t tests comparing differences in mean of treatment group to mean in placebo group.
**Acetazolamide taken outside study protocol or ≥3 consecutive study doses missed.

Table 3 Ascent rate, compliance, and side effects of groups receiving prophylactic agents for acute mountain sickness. Values are numbers (percentages) unless stated otherwise

Variables	All participants (n=487)	Placebo group (n=119)	Acetazolamide group	Odds ratio (95% CI)*	Ginkgo group (n=124)	Odds ratio (95% CI)*	Combined acetazolamide and ginkgo group (n=126)	Odds ratio (95% CI)*
Acclimatisation nights:								
Baseline†	348 (71)	85 (71)	81 (69)	1.14 (0.65 to 1.99)	93 (75.0)	0.83 (0.47 to 1.47)	89 (71)	1.04 (0.60 to 1.81)
Midpoint (4595 m)	95 (19)	24 (20)	26 (22)	0.89 (0.48 to 1.67)	14 (11.3)	1.98 (0.97 to 4.05)	31 (25)	0.77 (0.42 to 1.42)
Doses missed	33 (7)	7 (6)	9 (8)	1.16 (0.34 to 3.90)	5 (4.0)	1.59 (0.44 to 5.80)	12 (9)	0.76 (0.26 to 2.27)
Paraesthesias	200 (41)	12 (10)	85 (72)	0.04 (0.02 to 0.09)	10 (8.1)	1.28 (0.53 to 3.08)	93 (74)	0.04 (0.02 to 0.08)
Blurred vision	7 (1)	3 (2)	0 (0)	NA	2 (1.6)	0.64 (0.18 to 19.16)	2 (2)	0.62 (0.18 to 19.48)
Rash	7 (1)	1 (1)	0 (0)	NA	0 (0.0)	NA	6 (5)	0.17 (0.01 to 1.44)
Frequency	21 (4)	2 (2)	10 (8)	0.18 (0.04 to 0.86)	2 (1.6)	1.04 (0.14 to 7.52)	7 (6)	0.29 (0.06 to 1.43)
Dysgeusia	33 (7)	3 (2)	13 (11)	0.21 (0.06 to 0.75)	6 (4.8)	0.51 (0.12 to 2.08)	11 (9)	0.27 (0.07 to 0.99)

*Compared with incidence in placebo group.
†Two nights.

clinical effect closely in line with previous studies.[16 17] These results validate acetazolamide therapy as the standard of care for pharmacological prevention of acute mountain sickness, which may be used as an adjunct to behavioural strategies for avoiding altitude sickness. The substantial clinical effectiveness of the acetazolamide 250 mg twice daily regimen in this trial is also important in light of the group's previous results from a randomised trial of similar design, which utilised acetazolamide 125 mg twice daily and also showed significant protection against acute mountain sickness. The combined data from these prospective studies clearly counter the results of a meta-analysis published previously, which suggested that at least 750 mg of acetazolamide daily is required for adequate prophylaxis against acute mountain sickness.[17 18]

Limitations of the study

Our study had several limitations. Firstly, baseline was at a high elevation (4280 m or 4358 m); many participants will have acute mountain sickness below this altitude, and hence it is difficult to compare our results with those of other studies that had a low baseline altitude. Although it may be argued that participants who achieve ascent to this altitude are relatively resistant to acute mountain sickness, these individuals were protected from acute mountain sickness using acetazolamide in a manner that was consistent with previous studies, suggesting that testing conditions were adequate.[16 17] Secondly, just over a fifth of participants were lost to follow up, and the outcome among these people may have affected the significance of our findings. However, participants in all groups were equally likely to drop out of the study, and a reasonable degree of attrition is expected (and consistent with previous studies) owing to the wilderness setting and the low incentive to follow up at the study end point.[14 16 17] Thirdly, participants were recruited at two villages situated in close proximity, with around 78 m difference in elevation, which may differentially influence the degree of exposure to hypoxia. We did not, however, consider this important, as judged by the lack of any statistically significant differences in groups for personal characteristics or outcome measures (data not shown). Lastly, although we studied a diverse population in typical trekking conditions, these results may not be generalisable to other high altitude trekking environments where ascent rates and baseline elevation or final elevation may be different.

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Contributors: JHG wrote the original manuscript with the close consultation of the authors; he will act as guarantor for the paper. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. All authors were responsible for the study design with end stage input from BM Cogtry, AE Derrow, DJ Douglas, JY Meyer, AR Mulcahy, JD Ngo, CT Purgason, SG Seale, JL Snow, and H Zacharia. JO and JHG acquired the funding. JHG, BB, BM Cogtry, AE Derrow, DJ Douglas, JY Meyer, AR Mulcahy, JD Ngo, CT Purgason, SG Seale, JL Snow, and H Zacharia were responsible for the implementation of the study and data collection. JHG, BB, EWJ, JO, and PSH were responsible for data entry and analysis. JHG, BB, EWJ, JO, PSH, BM Cogtry, AE Derrow, DJ Douglas, JY Meyer, AR Mulcahy, JD Ngo, CT Purgason, SG Seale, JL Snow, and H Zacharia prepared and revised the manuscript.

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Ethical approval: This study was conducted under the auspices of the Himalayan Rescue Association and received ethical approval from the Nepal Health Research Council.

What is already known on this topic

Ginkgo biloba, an experimental prophylactic agent against acute mountain sickness, has shown mixed efficacy in several small randomised controlled trials

Acetazolamide is the standard pharmaceutical prevention of acute mountain sickness

The minimum effective dose of acetazolamide is under debate

What this study adds

This large randomised controlled clinical trial showed that ginkgo was not effective in decreasing the incidence or severity of acute mountain sickness

The efficacy of acetazolamide for preventing headache was decreased when combined with ginkgo

Acetazolamide at 500 mg daily had a robust clinical effect

Acetazolamide could be used as an adjunct to behavioural strategies for avoiding altitude sickness

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Amendment

This is version 2 of the paper. In this version the point estimate for incidence of acute mountain sickness with combined acetazolamide and gingko has been corrected and now reads 1.24 [instead of 12.4] and the third footnote in table 2 now reads ‡Lake Louise score ≥ 5 ["&period" has been removed].