ISRCTN28251193 https://doi.org/10.1186/ISRCTN28251193

A randomised double blind placebo controlled trial to ascertain the benefit of acetazolamide in the prevention of HAPE (High Altitude Pulmonary Edema)

Submission date
31/07/2006

Recruitment status
No longer recruiting

Registration date
01/08/2006

Overall study status
Completed

Last Edited
24/07/2013

Condition category
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
High altitude pulmonary edema (HAPE fluid accumulation in the lungs) is an illness that can cause death and can be seen in climbers when hiking at elevation higher than 3000 m. HAPE happens when trekkers ascend too quickly without giving their bodies enough time to adjust to the decrease in oxygen. HAPE happens in around 5-15% of walkers and trekkers at elevation over 4000 m. Currently, the most commonly used drug to treat HAPE sometimes causes headache, which can worsen the problem rather than improve it. Acetazolamide is a drug used to fight similar sicknesses to HAPE like acute mountain sickness (AMS flu or hangover signs caused by low oxygen levels) and high altitude cerebral edema (HACE swelling of brain tissue from fluid leakage). Acetazolamide is not expensive and is commonly used. However, there have been no human studies to see if acetazolamide could be used to fight HAPE. The goal of this study is to see if acetazolamide can prevent HAPE in climbers at high elevation, to see if acetazolamide will reduce lung artery pressure, and to observe AMS, HAPE and HACE in climbers.

Who can participate?
The study aims to recruit 500 healthy adults between the ages of 18 and 65, male or female, non-Nepali, and without AMS already. Adults may not be already taking any drug for the prevention of altitude illness. Adults will be recruited while on their way to Everest Base Camp or Kala Patthar, between the villages of Pheriche/Dingboche and Lobuje.

What does the study involve?
Volunteers will be randomly allocated into one of two groups. One group will receive a four-day supply of 250 mg of acetazolamide to be taken twice per day, and the other group will receive a dummy drug (placebo). Volunteers will be recruited at Pheriche, at elevation of 4300 m, and basic vital signs will be measured at that time. Vital signs will be measured again between 36-96 hours after having taken acetazolamide in Lobuje, at elevation of 5000 m. A variety of other tests will be also be conducted before and after having taken the study drug: a questionnaire testing for signs of altitude sickness, amount of oxygen in the volunteers blood, blood pressure,

heart rate, lung examination via stethoscope, and examination of heart vessels through sound waves. Data will also be collected on the kinds of people participating in the study at the enrolment site. Examples of body signs asked for on the questionnaire include chest tightness, coughing and tiredness. The tests conducted will show whether trekkers have AMS, HAPE or HACE and if so, the seriousness of the sickness.

What are the possible benefits and risks of participating?
Possible side effects of acetazolamide include tingling feeling of the skin, more urination than normal, and indigestion allergic reactions are extremely rare. The study will give all participants access to medical care for at least 24 hours after taking the drug. This research team has a strong safety record working with trekkers in the Everest region, with three studies since 2002 using similar protocols. Only two people out of a total of 1065 trial participants in those three studies needed care due to mild rashes from acetazolamide.

Where is the study run from?
The study is run by researchers at the Oxford University Clinical Research Unit (Nepal), Himalayan Rescue Association/Nepal International Clinic (Nepal) and Stanford University (California, USA).

When is study starting and how long is it expected to run for?
The study ran from October to November 2006 for a total of 2 months. The study has been completed.

Who is funding the study?
The Wellcome Trust (UK).

Who is the main contact?
The Clinical Trials Unit at the Oxford University Clinical Research Unit Viet Nam. +84839241983

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OXTREC 002-06

Study information

Scientific Title

Acronym
HAPE prevention trial

Study objectives
High Altitude Pulmonary Edema (HAPE) is a life-threatening illness seen in trekkers, climbers, pilgrims, porters and other high altitude (more than 3000 m) sojourners. HAPE usually results from ascending too high too fast, but people may also be predisposed to this at high altitude either genetically or due to a concurrent illness like an upper respiratory tract infection or any mechanism that increases the pulmonary artery pressure, for example mitral stenosis. Increase in Pulmonary Artery Pressure (PAP) is considered to be essential in the diagnosis of HAPE, and hypoxia is a strong trigger for enhancing PAP.

We hypothesise that HAPE incidence is around 5 - 15% at altitude at 4000 m or more although no recent figures are available. The calcium channel blocker nifedipine due to its action of decreasing PAP has been shown to work in the prevention and treatment of this potentially fatal illness. However because nifedipine causes hypotension and dizziness which may be an uncommon but disturbing side effect in the mountains, this drug is not readily used for the prevention of this illness. The specific phosphodiesterase inhibitor sildenafil which also decreases PAP through a different mechanism is a candidate drug for the prevention of HAPE but because its common side effect is headache, there will be a reluctance to use this drug even if shown to be effective. High altitude headache is already a common problem in the mountains regardless of drug ingestion.

Acetazolamide, an inexpensive, well tolerated and commonly used drug at high altitude for the prevention and treatment of Acute Mountain Sickness (AMS) and High Altitude Cerebral Edema (HACE) has amazingly not been studied in the prevention of HAPE. Intuitively there would seem to be at a minimum some shared pathophysiological mechanism based on hypoxia between AMS and HAPE. Recently some animal studies have shown the efficacy of acetazolamide in decreasing PAP. However there have been no studies using acetazolamide in the prevention of HAPE. The mechanism of action of decreasing PAP by acetazolamide does not seem to be related to carbonic anhydrase inhibition caused by acetazolamide but rather its proposed action is at the level of Ca(2+) release from the sarcoplasmic reticulum, a process which initiates and amplifies cell membrane Ca(2+) channel opening.

The aims of the study are as follows:
1. To see if acetazloamide 250 mg twice daily is effective in the prevention of HAPE.
2. To ascertain if acetazolamide will influence Pulmonary Artery Systolic Pressure (PASP) after ascending to 5000 m from 4300 m.
3. To determine the incidence of AMS, HAPE, and HACE in this cohort that will ascend to 5000 m.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Prospective two-armed double-blind randomised placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
High altitude pulmonary edema

Interventions
Computer generated randomisation will have been carried out. After consent is obtained, participants will receive either acetazolamide 250 mg twice daily or visually matched placebo twice daily. Trekkers will be enrolled and baseline study done at 4300 m (Pheriche) and re-assessed at the endpoint 5000 m (Lobuje). The reassessment will take place at least 36 hours (to four days) after taking the first study drug.

The approach to Everest Base Camp provides a unique study population for the following reasons:
1. Large numbers of recently arrived (non-acclimated) trekkers
2. Relatively homogenous population (gender, age, physical fitness, etc.) with relatively few pre-existing conditions
3. Linear population movement along the approach
4. Rapid and quantitatively large elevation change (about 700 m)

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Acetazolamide

Primary outcome measure
1. Evaluation for HAPE in study participants will be made by study administrators after a minimum of 15 minutes of rest. Study administrators will have had prior experience taking vital signs and performing lung examinations. Diagnosis of a participant with or without AMS will be made only if two of the following signs and two of the following symptoms are present:
a. Symptoms: chest tightness, cough, dyspnea at rest, markedly decreased exercise performance (LLQ fatigue score of three)
b. Signs: central cyanosis, pulmonary crackles, tachycardia (more than 110 beats per minute), tachypnea (more than 25 revolutions per minute)
2. Doppler echocardiography will be performed also after 15 minutes of rest by trained echocardiographers. Cutoff criteria for HAPE will be the measurement of pulmonary artery systolic pressure of 48 mmHg or greater via transtricuspid pressures) with normal left ventricular wall motion and function

Secondary outcome measures
1. Pulse oxygen saturation of less than 70% in subjects meeting HAPE diagnosis
2. The change in PAP from 4300 m to 5000 m or the delta PAP will be measured and compared between placebo and acetazolamide groups
3. Incidence of AMS, HAPE, and HACE in this cohort of people ascending from 4300 m to 5000 m in the Khumbu region

Overall study start date
01/10/2006

Completion date
30/11/2006

Eligibility

Key inclusion criteria
1. Healthy men or women between the ages of 18 and 65 without any current illness, travelling DIRECTLY to either Mount Everest base camp or Kala Patthar, not using any drugs for the prevention of altitude sickness.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants

250 in each arm (total = 500)

Key exclusion criteria
1. Younger than 18 years old or 65 years or older
2. Trekkers going to Gokyo, Chukung Ri, or Island Peak BEFORE going to Kala Patthar or Everest base camp
3. Altitude sickness (more than one mild symptom on the Lake Louise Questionnaire [LLQ]) or significantly depressed oxygen saturation (less than 75%)
4. Pregnant woman or women who cannot exclude the possibility of being pregnant, or have missed menses by over seven days
5. A known drug allergy to acetazolamide or other sulfa drugs
6. Have already stayed the night at an altitude of 4500 m/14000 ft within the last nine days
7. Have taken any of the following in the last two days: acetazolamide (diamox®), steroids (dexamethasone, prednisone), theophylline, or diuretics (lasix®), viagra, nifedipine
8. Have any serious intracranial abnormalities such as history of brain tumors or pseudotumour cerebri or any known cardiac or lung disease

Date of first enrolment
01/10/2006

Date of final enrolment
30/11/2006

Locations

Countries of recruitment
Nepal

Study participating centre
Himalayan Rescue Association\Patan Hospital
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Nepal
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Funder(s)

Funder type
Charity

Funder Name
The Wellcome Trust (UK) (grant ref: 061330)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration