

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

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<b>Registration date</b> 01/08/2006	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 24/07/2013	<b>Condition category</b> Respiratory	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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

### Contact name

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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  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum, a process which initiates and amplifies cell membrane  $\text{Ca}^{2+}$  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\Patana Hospital

Kathmandu

Nepal

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## **Sponsor information**

### **Organisation**

University of Oxford (UK)

### **Sponsor details**

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**ROR**  
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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