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# Study of Safety Assessment of Acetazolamide in Prevention of High-Altitude Illness

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**Abstract:** ***Background**: High altitude illness (HAI) poses a significant risk to individuals ascending rapidly to high altitudes. Acetazolamide is widely used as a prophylactic agent to prevent HAI. However, comprehensive safety data in large populations remain limited. **Objective**: To assess the safety profile of Acetazolamide in the prevention of high-altitude illness through evaluation of side effects in a large study population. **Methods**: A total of 5, 503 participants who were willing to receive Acetazolamide were included in the study. Drug administration consisted of either a single dose of Acetazolamide 250 mg SR or Acetazolamide 125 mg twice daily. Participants were monitored for six days for the development of side effects. **Results**: Of the 5, 503 participants, 568 (10.32%) manifested one or more side effects. The most commonly reported side effects were tingling (4.29%) and dry mouth (2.13%). Severe side effects were rare. **Conclusion**: Acetazolamide was well tolerated in the majority of individuals. Most side effects were mild and self-limiting, supporting its continued use as a prophylactic agent for HAI with appropriate counselling.*

**Keywords:** High Altitude, Adverse Effects

## 1.Introduction

High altitude (HA) areas are defined as areas at altitudes equal to or greater than 2700 meters above mean sea level. At this altitude and beyond, alterations in human physiological function become apparent. The alveolar partial pressure of oxygen (PaO2) at 2700 meters is about 60mmHg and the corresponding arterial oxygen saturation (SPo2) is 90 %. (1)

However, informed decision making about whether to use AZM (and if so which dose) is based on weighing potential *benefits* against *risks*, and thus requires robust quantitative estimates for each. Furthermore, whether efforts to find the lowest effective dose of AZM for other conditions (e.g., idiopathic intracranial hypertension and sleep apnoea) are warranted depends on whether side effects are dose-dependent.

This perception has led to substantial efforts to find the lowest effective dose to prevent AMS for which a review from 2012 suggested 250 mg/day to be similarly effective as 750 mg/day.

**Understanding Acetazolamide**

Acetazolamide is a key medicine for altitude sickness, known scientifically as acetazolamide. It works well for high places where mountain sickness often happens.

**What is Acetazolamide?**

Acetazolamide belongs a group of drugs called carbonic anhydrase inhibitors. Doctors prescribe it for glaucoma, epilepsy, and swelling. Its main use, though, is to help with mountain sickness. It works by stimulating increased breathing rate through acid-base balance adjustments, thereby improving oxygenation and helping the body acclimatize more rapidly to higher altitudes. When taken correctly, it can significantly reduce the likelihood of developing altitude sickness, especially if started before ascent and continued during the period of exposure to high elevation. (2). Typically, the medication is initiated one to two days before ascending to high elevations-usually above 8, 000 feet (2, 400 meters) -and continued for a few days after reaching the target altitude. The common dosage for prophylaxis is 125 mg twice daily, but this may vary depending on individual health conditions and advice from a healthcare provider. (3, 4)

How Does Acetazolamide Work?

Acetazolamide makes the kidneys get rid of more bicarbonate, which makes the blood more acidic. This leads to better and faster breaths. Breathing better helps get more oxygen and can make you feel better at high places. It works by blocking a natural chemical in the body that helps make fluid in the eyes, brain and kidneys. By doing this:

- It lowers pressure in the eyes (helps in glaucoma).
- It controls unusual brain activity (helps with some types of seizures).
- It helps remove extra water and salts through urine.

It helps your body adjust to high altitudes and prevents Acetazolamide altitude sickness.

It's very important to take Acetazolamide the right way. How much you need changes based on your health.

**Common Side Effects (3)**

Side effects are common with some studies reporting an incidence of 80%-100% which limits patients' tolerance and compliance. It has been postulated that some of the side effects may be related to the amount of metabolic acidosis caused by AZM (via renal bicarbonate wasting which reaches steady state within 1-2 days) and plasma drug levels that are affected by weight and renal function. Severe side effects were rare and largely confined to subgroups of patients: that is, hypokalaemia almost exclusively in patients on thiazide diuretics or angiotensin-receptor blockers which is consistent with reports from non-included studies, metabolic acidosis in 'sicker' hospitalised patients, dyspnoea in patients that have already an increased work of breathing due to their underlying condition. (5)

- Fatigue and drowsiness
- Loss of appetite
- Nausea or vomiting
- Mild dizziness
- Diarrhoea
- Altered taste, especially for carbonated beverages
- Numbness or tingling in the hands and feet
- Increased Urination

**Serious Side Effects**

Some serious side effects of Acetazolamide need fast medical help. These include:

- Severe allergic reactions like rash, itching, or swelling, mainly in the face/tongue/throat
- Difficulty in breathing
- Severe dizziness or fainting
- Unusual tiredness or weakness
- Persistent nausea and vomiting
- Changes in kidney function, shown by trouble urinating or blood in urine
- Signs of liver disease, including yellow eyes or skin (jaundice), dark pee, or stomach pain
- Yellow Tinge to the eyes
- Confusion /Irritability
- Sudden Blurring of vision
- Stevens-Johnson Syndrome (SJS): Painful red/Purple rash with blisters, mucosal involvement (mouth/eyes/genitals), Fever
- Severe Metabolic Acidosis: Deep rapid breathing, Confusion
- Haematological Effects: Aplastic Anaemia, Agranulocytosis

**Contraindicated**

- Kidney or liver disease
- Metabolic acidosis
- Allergy to sulphonamides and sulphonamide derivatives
- Low blood levels of sodium and/or potassium; high chloride levels
- If you are pregnant, think you may be pregnant or are planning to become pregnant
- Reduced function of adrenal glands or Addison's disease
- Breastfeeding
- Kidney stones
- Lung or any problems with breathing (COPD, chronic bronchitis, emphysema)
- Diabetes mellitus. Acetazolamide can affect blood sugar control.
- If you are taking aspirin, warfarin, blood pressure medications, steroids, metformin, gliclazide, lithium, methenamine, methotrexate, valproate, zonisamide, ciclosporin, sodium bicarbonate, digoxin, amphetamines, quinidine or medication for epilepsy

**Objective**

Our objective is to provide precise estimates for the risk of developing one of the common side effects of AZM and to assess systematically whether this risk is dose-dependent.

**Methods**

This review was performed according to a pre-specified study protocol (online supplementary e-Appendix 1) and following PRISMA-reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

**Study**

What is the key question?

- What is the risk of developing one of the common side effects of AZM and are these risks dose-dependent?

**Identification of studies**

The study is an observational study in which a select population is given Acetazolamide and side effects are noted.

**Inclusion Criteria**

The individuals who reported any side effects have been noted.

**Exclusion Criteria**

Trials with subjects who were non-human, non-adult, unable to report side effects reliably (eg, intubated), receiving haemodialysis (rationale: substantial impact on pharmacokinetics; high prevalence of dysgeusia, paraesthesia/neuropathy, fatigue; inability to assess polyuria) have been excluded.

## 2.Methodology

### 2.1 Study Design and Population

This was an observational safety assessment study conducted on a population undergoing high altitude exposure.

Total Participants (Willing): 5, 503
Number Unwilling / Declined participation: 329 (excluded from analysis)

1. Tab Acetazolamide 250 mg SR Single dose or
2. Tab Acetazolamide 125 mg x 2 tablets
3. Monitoring for six days for side effects

### 2.2 Drug Administration

Participants were administered one of the following regimens:

1. Acetazolamide 250 mg SR - Single dose daily
2. Acetazolamide 125 mg - Two tablets daily (total 250 mg/day)

### 2.3 Monitoring Period

Participants were monitored for six days following drug administration for the development of any side effects or adverse events.

### 2.4 Data Collection

All reported side effects were documented systematically. The frequency and percentage of each side effect were calculated relative to the total number of participants who received Acetazolamide.

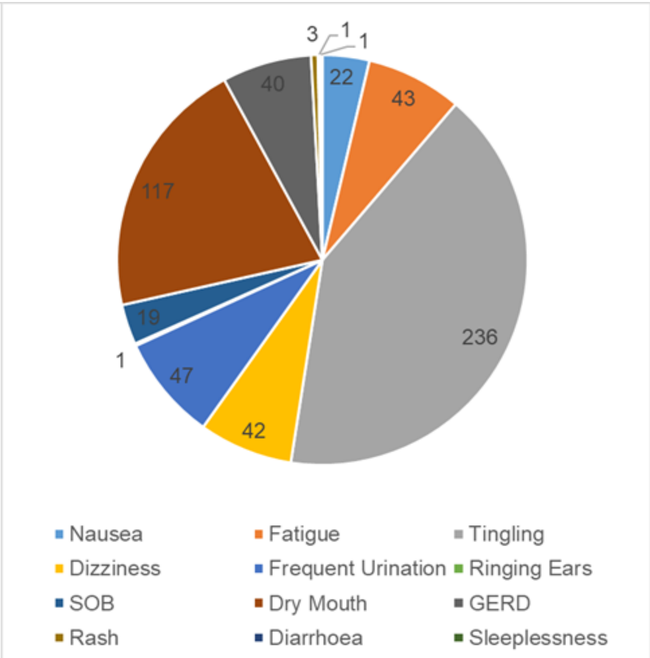
**Side Effects of** Acetazolamide: Number of indvls in the study population reporting Side Effects.

## 3.Results

### 3.1 Incidence of Side Effects

Out of 5, 503 participants, 568 individuals (10.32%) reported at least one side effect during the monitoring period.

| Side Effect | Number of Cases | Percentage (%) of Total Participants |
|---|---|---|
| Nausea | 22 | 0.40 |
| Fatigue | 43 | 0.78 |
| Tingling | 236 | 4.29 |
| Dizziness | 42 | 0.76 |
| Frequent Urination | 47 | 0.85 |
| Headache | 0 | 0.00 |
| Ringing in Ear | 1 | 0.02 |
| Streaks of Blood | 19 | 0.35 |
| Dry Mouth | 117 | 2.13 |
| Gastroesophageal Reflux Disease (GERD) | 42 | 0.76 |
| Diarrhoea | 1 | 0.02 |
| Sleeplessness | 1 | 0.02 |




## 4.Discussion

This comprehensive meta-analysis of low-to-moderate quality evidence defines the risk of common AZM side effects and corroborates the adverse effects paraesthesia, dyspepsia and possibly fatigue are dose-dependent. The most frequent side effect-tingling-was consistent with known pharmacologic effects of Acetazolamide related to its carbonic anhydrase inhibition. Similarly, polyuria and dry mouth are expected diuretic effects of the drug.

Importantly, no significant neurological or severe gastrointestinal side effects were observed. The absence of headache as a reported side effect is notable, particularly because headache is often a symptom of high-altitude exposure itself rather than a drug reaction.

These findings align with previously published literature indicating that Acetazolamide is generally safe for prophylactic use at recommended doses. The low incidence of serious side effects supports its widespread use in high-altitude expeditions, with appropriate patient education regarding expected sensations such as tingling and increased urination.

Common and early occurring dose-dependent adverse reactions to AZ include peripheral paraesthesia (notably a tingling sensation in the hands and feet), increased urination (polyuria), dry mouth, loss of appetite, altered taste, particularly of carbonated beverages, and tinnitus. Less common are nausea, headache, and dizziness, which can unfortunately mimic the symptoms of AMS itself as well as GI distress, and possibly occasional drowsiness and confusion). Severe side effects were rare and not significantly reported. Moderate but rarer, events include ocular effects such as ringing in ears. (6) Paraesthesia, dysgeusia and possibly fatigue are likely dose-dependent phenomena and may thus be avoidable by using low-dose AZM and respond to dose reduction; on the other hand, some gastrointestinal symptoms may reflect local irritation and thus be ameliorated by administering AZM with food. Severe side effects are rare and can largely be avoided by careful patient selection (e.g. hypokalaemia occurs almost exclusively in patients co-treated with thiazide diuretics or angiotensin receptor blockers).

Differentiation from symptoms of AMS: AMS symptoms include Headache, Nausea, Dizziness, Fatigue and Sleep disturbance.
In AMS headache and dizziness is associated with ataxia /confusion.

**Management of Side Effects**

1. Tingling, Taste Change, GI Upset: **Reassure, Hydrate, Antacids**
2. Rash, Persistent GI Upset: Stop Acetazolamide. Antihistamines, ORS
3. Stevens-Johnson syndrome: Stop Acetazolamide immediately. ICU Care. Antibiotics, IV Fluids
4. Anaphylaxis: Adrenaline 0.5 mg IM (1: 1000)
   a. Oxygen Supplementation
   b. IV Fluids
   c. Inj. Hydrocortisone 100 mg IV Stat
   d. Inj Chlorpheniramine 10 mg IM/Slow IV
5. Severe Metabolic Acidosis: Stop Acetazolamide
   a. IV Sodium Bicarbonate
   b. Refer to Higher Center

## 5. Recommendation

The goal of the present review was to focus on side effects of AZ taken as prevention in high altitude area.

Using Acetazolamide for altitude sickness needs special care. You should always check with a doctor first. The dose you need depends on your health, where you're going, and other health issues. Normally, people take 125 mg to 250 mg twice a day to avoid or treat sickness.

It's best to start 1 or 2 days before the climb and keep taking it for 2 days after stopping climbing. This lets the body get used to the lower oxygen. It makes getting sick less likely.

| Purpose | Recommended Dosage | Frequency | Purpose |
|---|---|---|---|
| Prevention | 125-250 mg | Twice Daily | Prevention |
| Treatment | 250 mg | Twice Daily | Treatment |

Reviewed evidence relative to four doses of AZ (125, 250, 500, and 750 mg daily), with regard to their ability to decrease the incidence and severity of AMS during rapid ascent to altitudes >3, 500 m. Although earlier studies used higher doses, it appears that lower doses have become more common in recent decades and that 250 mg/day is sufficient for the majority of people during moderate rates of ascent to lower altitudes (i. e., <3, 500 m). However, based on the present review, the military, emergency medical personnel, or others who must ascend rapidly to altitudes above 3, 500 m and immediately perform specialized tasks may require dosing of 500 or 750 mg/day. (6, 7)

The efficacy of prophylactic AZ was directly proportional to the baseline risk of AMS (i. e., low AZ efficacy linked to low risk of AMS), suggesting that more rapid ascents (with higher risk of development of AMS) would benefit from higher doses (500-750 mg/day). AZ in daily doses of 250 and 500 mg provided slightly better efficacy with preventing AMS over other interventions. (8)

Side Effects to look for and report on priority.

1. Allergic Reactions: Skin rash, itching
2. Unusual weakness, fatigue, breathlessness. These could be suggestive of Aplastic Anaemia
3. High acid level. Trouble breathing, unusual weakness and fatigue
4. Infection, Fever, Chills
5. Blood in urine or trouble passing urine suggestive of kidney stones
6. Pain in right upper belly, loss of appetite, light coloured stool, dark brown urine, yellowing skin or eyes.
7. Muscle Cramps suggestive of low potassium
8. Redness, blistering or loosening of the skin including mouth

## 6. Conclusion

Acetazolamide is a safe and well-tolerated prophylactic medication for high altitude illness in healthy individuals.

- 10.32% of participants experienced mild side effects.
- Tingling and dry mouth were the most commonly reported adverse effects.
- No severe or life-threatening adverse events were noted.

Proper counselling regarding expected mild side effects can improve compliance and preventive outcomes. Acetazolamide remains a reliable and safe agent for high altitude prophylaxis.

The most common side effects of AZM are paraesthesia, Tingling and Dry Mouth which may reduce therapy compliance. Other common side effects such as fatigue and gastrointestinal symptoms. Paraesthesia, dysgeusia and fatigue gastrointestinal symptoms may reflect local irritation and thus be ameliorated by administering AZM with food. In select cases, side effects may alternatively be mitigated by use of an alternative CA inhibitor or bicarbonate supplementation. (9)

Severe side effects are rare and can largely be avoided by careful patient selection (e.g., hypokalaemia occurs almost exclusively in patients co-treated with thiazide diuretics or angiotensin receptor blockers).

This review complements data about AZM safety, thus facilitating a more balanced assessment of AZM's clinical value.

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**Appx A**

**Assessment of Side Effects of Acetazolamide**

**1. Details of Individual:** Name, Age, Sex

| S. No | Side Effects | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1. | Nausea | | | | | | | |
| 2. | Fatigue | | | | | | | |
| 3. | **Tingling** | | | | | | | |
| 4. | Dizziness | | | | | | | |
| 5. | Frequent Urination | | | | | | | |
| 6. | Headache | | | | | | | |
| 7. | Ringing in Ear | | | | | | | |
| 8. | Streaks of Blood | | | | | | | |
| 9. | **Dry Mouth** | | | | | | | |
| 10. | Gastro Oesophageal Reflux Disease | | | | | | | |
| 11. | Diarrhoea | | | | | | | |
| 12. | Sleeplessness | | | | | | | |
| 13. | Rash | | | | | | | |
| 14. | Dry Mouth | | | | | | | |