STUDY PROTOCOL[1]

Title: Side Effects of Acetazolamide: A Systematic Review and Meta-Analysis Assessing Overall Risk and Dose-Dependence

Registration: none

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INTRODUCTION:

Rationale: Acetazolamide has been used since the 1950s for various conditions.[2-8] E.g. it has been found to be highly efficacious in reducing glaucoma and preventing acute mountain sickness (AMS); however, side effects are common (in some studies 80-100%[3,9], especially paresthesias, taste disturbances, polyuria and fatigue) and may limit patients' tolerance/compliance.[3,10] It has been postulated that some of the side effects may be related to the amount of metabolic acidosis caused by acetazolamide[11] (via renal bicarbonate wasting which reaches steady-state within 1-2days[12]) and plasma drug-levels which are affected by weight and renal function[13-15]. Based on data limited by small numbers and/or observational nature there has been a notion that some of the side effects may be dose dependent.[16,17] This led to substantial efforts to find the lowest effective dose to prevent AMS for which a recent review suggested 250mg/day to be similarly effective as 750mg/day,[16] although the number needed to treat was higher for the lower dose (NNT 6 [95%-CI 5-11] vs 3 [95%-CI 3-5]). Informed decision making about whether to use acetazolamide (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 acetazolamide for other conditions (e.g. idiopathic intracranial hypertension and sleep apnea) are warranted depends on whether side effects are dose-dependent.

Objective: To provide a precise estimate of the overall risk of developing one of the common side effects of acetazolamide and to assess systematically whether this risk is dose-dependent.

METHODS

Eligibility Criteria:

Inclusion Criteria (PICO):

Any Randomized Controlled Trial in which adult subjects are randomized to oral acetazolamide vs placebo reporting side effects (especially paresthesia, dysgeusia, polyuria).

Exclusion Criteria:

- non-human subjects
- non-adult
- subjects unable to report symptoms (e.g. intubated)
- subjects on hemodialysis (heavily affects plasma levels of acetazolamide and frequently causes symptoms similar to the main side effects such as paresthesias and taste disturbances, while polyuria cannot be assessed)
- administration of acetazolamide in other than PO (e.g. IV, inhaled; d/t likely different pharmacodynamics)
- co-administration of other interventions that may confound side effects (e.g. acetazolamide+dexamethasone)

Information Sources:

- MEDLINE since inception
- EMABSE since inception
- Review of reference lists of retrieved articles and other relevant articles
- Clarification form authors may be sought as needed

Search Strategy:

MEDLINE:

(Acetazolamide[Mesh] OR Acetazolamide[tiab]) AND (Randomized Controlled Trial[ptyp] AND Placebo)

EMBASE:

('acetazolamide':ti,ab,kw OR 'acetazolamide'/exp) AND ('placebo':ab,ti OR 'placebo'/exp) AND ('randomized controlled trial'/de)

Data Management:

- Excel Sheet for data entry and storage
- STATA for analysis

Selection Process

If possible eligibility will be done independently by two reviewers (final eligibility based on consensus agreement) and abstracted data/bias assessment will be checked by a second reviewer

Data Collection process

- Entry into Excel Sheet using validation criteria (e.g. drop down lists whenever possible)
- Clarification of data with authors if needed and possible

Data items

General Infos:

- First Author name
- Publication Year
- Condition (i.e. targeted condition in the trial; e.g. healthy volunteers vs sleep apnea, acute mountain sickness, etc)

- High Altitude (i.e. study performed at >2000m)
- Cross-over vs Parallel group trial
- Wash-out days (for cross over trials)

Intervention Details:

- Total Daily Dose of Acetazolamide
- Number of Acetazolamide doses/day
- Days of Acetazolamide administration

Potential Effect modifiers:

- Percent Females
- Mean Age
- BMI
- Weight
- Race (Percent white, black, other)
- Diuretic use
- Adjustment of Dose by renal function
- Co-administration of potassium
- Lab values (at the end of placebo or acetazolamide administration):
    - pH
    - pO2
    - pCO2
    - Bicarbonate
    - Chloride
    - Sodium
    - Potassium
    - Creatinine
- Mode of Side effect assessment (active vs passive/unclear)

Outcomes - Side Effects* (numbers/persons):

- Main:
    - Paresthesia
    - Taste Disturbance
    - Polyuria
    - Fatigue
- Others:
    - Thirst
    - Pollakiuria
    - Nocturia
    - Nephrolithiasis
    - Hypokalemia
    - Depression
    - Dizziness
    - Tinnitus
    - Nausea
    - GERD

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- Vomiting
- Anorexia
- Diarrhea
- GI discomfort
- Transaminitis
- Dyspnea
- Rash
- Hematologic Dyscresias
- Others if reported and plausibly related to acetazolamide

Outcomes and prioritization:

- Main Outcomes (based on what has frequently reported* in the literature[3,16,17]):
  - Paresthesia:
    - numbness or tingling of face or limbs
  - Taste Disturbance:
    - change in taste including abnormal taste of carbonated beverages or metallic taste
  - Polyuria:
    - Excessive urination based on definition in primary study (including pollakiuria or nocturia if not reported separately from polyuria)
  - Fatigue:
    - (Psychological) Fatigue based on definition in primary study

*GI disturbances have also been frequently reported in the literature but due to the heterogeneity of "GI disturbances" (e.g. anorexia, nausea, vomiting, diarrhea, GERD) these will be collected and reported separately

- Other Outcomes:
  - Specified symptoms as above (informed by extensive report of side effects in a recent large RCT[8])
  - Any other side effect reported in a study that plausibly is due to acetazolamide

Risk of bias in individual studies:

Assessment of 5 bias domains as per Cochrane Handbook, Chapter 8 (http://handbook-5-1.cochrane.org/):

- Selection Bias
- Performance Bias
- Detection Bias

- Attrition Bias
- Reporting Bias

as Low vs Unclear vs High

Effect of bias on results will be tested by doing a sensitivity analysis checking for "effect modification" by bias strata.

Data Synthesis:

Pooled Effect Estimates:

For outcomes with data from 3+ studies a pooled effect estimate will be calculated using Mantel-Haenszel methodology (fixed effects model) based on odds ratios (rationale: better mathematical properties in this setting of likely variable event rates with some likely close to 100%, in which case risk ratio would give most weight to those; to aid interpretability final odds ratios will be translated into risk ratios based on event rate in the control group)[18] after adding a continuity correction. Studies with clearly stated "0" outcomes in both arms will be included on the premise that exclusion of such studies would otherwise bias results towards more extreme values (i.e. overestimate risk of a given symptom).[19]

If there is more than low amount of heterogeneity (i.e. moderate I^2 > 30% [Cochrane Handbook 9.5.2; http://handbook-5-1.cochrane.org/]) then attempts will be made to identify/account for the source of heterogeneity through stratified meta-analysis/meta-regression assessing primarily variables in the following order

- Acetazolamide dose primarily as total daily dose [TDD] and days of acetazolamide [DA] (potential exploration of or daily dose/kg [DDK], TDDxDA or DDKxDA)
- Mode of Data Abstraction (Active vs not)
- Condition; High Altitude
- Bias (Low vs unclear/high)
- Underlying Event rate

If heterogeneity remains high then additional factors may be explored in a post-hoc fashion.

If heterogeneity remains very high (I^2>50%) then no pooled estimate will be reported and instead a narrative summary will be attempted.

If heterogeneity remains moderately high (I^2 30-50%) then a random effects model (DerSimonian-Laird) will be used instead of the fixed effects model.

Effect Modification/Subgroup Analysis:

Primary:

One primary objective is to assess if side effects increase in a dose dependent manner, thus for all outcomes with a pooled effect estimate we will assess via meta-regression if there is effect modification by*

- total daily dose [TDD]
- Potential exploration of daily dose/kg [DDK], days of acetazolamide [DA], and TDDxDA or DDKxDA

* primary analysis will be based on the assumption that the possible relationship is linear but based on scatter-plot a quadratic relationship may be explored

Secondary:
To explore if side effects may be related to changes in physiology (i.e. to see if lab values could potentially be used to "predict" higher risk of side effects), for all outcomes with a pooled effect estimate we will assess via meta-regression if there is effect modification by lab values, especially:

- pH
- pCO2
- Bicarb (or Chloride as proxy)
- K

Similarly, to explore if side effects may be related to patient characteristics (i.e. to see if certain subgroups may be at higher risk, for all outcomes with a pooled effect estimate we will assess via meta-regression if there is effect modification by:

- Mean age
- Percent Females
- Race[3]

For Hypokalemia, effect modification by diuretics[9] will be assessed using meta-regression.

Interpretation of associations involving patient-level characteristics will carefully take into account the potential risk for ecological fallacies.

<u>Sensitivity Analysis:</u>

- Inclusion of studies that do not clearly report numbers for specific outcomes but state that generally no side effects were observed will be included for main outcomes
- Repeat main analysis based on "severe" side effects only
    - Definition of severe side effect for this review: side effect a.) results in dose reduction or discontinuation of acetazolamide; or b.) "severe/serious" per study definition
- Exclusion of studies using subjects with conditions that themselves cause the side effect of interest:

  - Acute Mountain Sickness (AMS): based on 2018 Lake Louise Acute Mountain Sickness Score defining symptoms are headache, GI sx (anorexia, nausea, vomiting), fatigue/weakness, dizziness/light-headedness.[20]
  - Chronic Mountain Sickness (CMS): Diagnosis of CMS is based on seven signs/symptoms (breathlessness and/or palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, headache, tinnitus) [7,21]
  - Idiopathic Intracranial Hypertension (IIH): based on modified Dandy criteria defining symptoms are headaches, nausea, vomiting, transient visual obscurations in awake and alert subjects. [22]
  - Pulmonary Hypertension (pHTN): dyspnea [per uptodate]
  - Acute or chronic respiratory failure: dyspnea
  - Glaucoma: Vision disturbances, headache
- Assessment of impact of eligibility and data abstraction decisions as needed
- Assessment of choice of effect measure (risk ratio [event = side effect occurs] vs odds ratio) for main outcomes
- Assessment of fixed vs random effects model for main outcomes

Other analyses:

- Number needed to harm will be assessed for each main outcome based on average event rare in control groups
- To inform about expected changes in physiology, for all lab values that are available from 3+ studies, a pooled effect estimate (weighted mean difference) will be attempted and effect modification by total daily dose will be explored.

Meta-Biases:

- Funnel Plot Assessment
- Eger's test (using $P<0.05$ to indicate publication bias or other source of heterogeneity)

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