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P: In individuals living at low altitude and going to high altitude.
I: Is the use of prophylactic pharmacological agents
C: Compared to no pharmacology.
O: Associated with a reduced risk of Acute Mountain Sickness.

Clinical scenario: 27 year old male 4th year medical student going from Detroit (approx 700 feet above sea level) to the Indian Himalayan mountains for a week of working in medical clinics at 5,000 feet and then trekking to 15,000 feet over the course of several days. Is there any drug that can be taken in advance to reduce the risks of developing AMS during the trek?

Background:

1,500-3,700m (5,000-12,000ft) = high altitude [Mt Rogers 5729 ft, highest point in Virginia]
3,700-5,500m (12,000-18,000ft) = very high altitude [Breckenridge, CO 12,998 ft; Vail, CO 11480 ft]
>5,500m (18,000ft) = extremely high [Mt. Everest 29,035 ft/8850m, tallest mountain in the world; McKinley (Denali), Alaska: 20,320ft/6194m, tallest mountain in U.S.]

Altitude sickness includes acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), and high altitude cerebral edema (HACE). AMS typically occurs above 2500m (8000 feet) [see addendum for signs and symptoms of AMS, HAPE, and HACE]. Symptoms of AMS develop over the course of hours to days depending on the rate of ascent and altitude attained. About 10-50% of non-acclimatized people will develop AMS above 3000m.

Acetazolamide is thought to prevent AMS and speed acclimatization by facilitating bicarbonate excretion, causing a mild metabolic acidosis, which helps offset the alkalosis produced by hyperventilation. Metabolic acidosis also stimulates the patient's ventilation to increase the rate and depth of breathing (thereby raising the arterial oxygen saturation) and alleviates fluid overload by acting as a diuretic. It hastens acclimatization and reduces the risk and severity of AMS. Adverse reactions include paresthesias, altered taste (especially a metallic taste to carbonated beverages), nausea, vomiting, anorexia, photosensitivity, urinary frequency, and drowsiness.

Dexamethasone may also be helpful in treating many of the symptoms of AMS and managing cerebral edema. It is not an alternative to acetazolamide since it does not affect respiration and does not speed acclimatization. Dosages are high (4 mg every 6 hours), which leads to unpleasant adverse reactions. If it is discontinued while the patient is still at a high elevation, symptoms may occur/recur.

Search strategy:
Medline 1999-2005 altitude and sickness (English and humans and reviews only)
Medline 1999-2005 altitude and sickness (English and humans meta-analysis only)
Medline 1999-2005 altitude and sickness and Diamox (English and humans only)
Medline 1999-2005 altitude and sickness and acetazolamide (English and humans only)
Medline 1999-2005 altitude and sickness and prevention (English and humans only)
Medline 1999-2005 acute and mountain and sickness (English and humans only)
Cocraine data base: altitude and sickness

Relevant papers:

Author, date	Patient group	Study type	Outcomes	Key results	Study

and country		(level of evidence)			weaknesses
Bailey DM, et al. 2001 UK	9 adults received high dose anti-oxidant vitamins and 9 adults got placebo	Randomized double-blind placebo-controlled	Lake Louis AMS score Arterial oxygen saturation Total caloric intake	2.8 +/- 0.8 points versus 4.0 +/- 0.4 points, P = 0.036 89 +/- 5% versus 85 +/- 5%, P = 0.042 13.2 +/- 0.6 MJ/day(-1) versus 10.1 +/- 0.7 MJ/day(-1), P = 0.001	Small sample size
Gertsch JH, et al. 2002 Hawaii, USA	26 participants residing at sea level received ginkgo biloba (60 mg TID) (n = 12) or placebo (n = 14) starting 24 h before ascent	double-blind, randomized, placebo-controlled trial	Lake Louis AMS score after 4 hours at max altitude	Two (17%) subjects on ginkgo and nine (64%) on placebo developed severe AMS (p = 0.021). Ginkgo use did not reach statistical significance for lowering incidence of AMS compared with placebo (ginkgo 7/12, 58.3% vs. placebo 13/14, 92.9%, p = 0.07). Twenty-one of 26 (81%) subjects developed AMS overall.	Outcomes assessed after only 4 hours which may be too early for AMS. Small sample size.
Basu M, et al. 2002 India	50 men were randomly divided into five groups of 10 each. Group I received prednisolone (Pred) 10 mg, Group II Pred 20 mg, Group III Pred 40 mg, Group IV dexamethasone 0.5 mg, Group V received placebo once a day in the morning for 2 days at sea level (SL) and for 3 days on arrival at an altitude of 3450 m by air.	Randomized clinical trial	Lake Louise AMS scoring system, blood pressure, respiratory rate, peripheral blood O2 saturation, and heart rate were measured at sea level and on arrival at high altitude	The steroid groups showed a significant reduction in daily AMS score as compared to placebo (P < 0.01). No change in heart rate, blood pressure, or pattern of oxygen saturation between steroids and placebo. Prednisone 20mg was the optimal dose for reduction of AMS score.	Treatment groups were small, results were not double-blinded.
Basnyat B, et al. 2003 Nepal	155 trekkers in the Himalayan mountains randomized to acetazolamide 125mg BID or placebo	prospective, double-blind, randomized, placebo-controlled trial	Lake Louis AMS score and pulse ox	There was a statistically significant reduction in incidence of AMS (placebo group, 24.7%, 20 out of 81 subjects; acetazolamide group, 12.2%, 9 out of 74 subjects). Prophylaxis with acetazolamide conferred a 50.6% relative risk reduction, and the number needed to treat in order to prevent one instance of AMS was 8. Of those with AMS, 30% in the placebo group (6 of 20) versus 0% in the acetazolamide group (0 of 9) experienced a more severe degree of AMS as defined by a Lake Louise Questionnaire score of 5 or greater (p = 0.14). Secondary outcome measures associated with statistically significant findings favoring the treatment group included decrease in headache and a greater increase in final oxygen saturation	Only 155 of 197 returned the survey.
Dumont L, et al. 2004 Switzerland	30 subjects received 400 mg of oral magnesium citrate (16 mmol) 31 received the placebo every 8 h for 5	Randomized clinical trial	Lake Louis AMS score	With oral magnesium, 20% of subjects had no AMS compared with 16.1% in the placebo group [RR (95% CI), 1.2 (0.4-3.6); where CI is confidence interval]. With magnesium, 40% were prevention failures	Small sample size

	days			compared with 35.5% in the placebo group [RR (95% CI), 1.13 (0.59-2.15)]. The mean time to failure and severity of AMS was similar between the two groups.	
Gertsch JH, et al. 2004 Arizona, USA	614 healthy western trekkers (487 completed the trial) assigned to receive ginkgo 120mg (n =157), acetazolamide 250mg BID (n =152), combined acetazolamide 250mg BID and ginkgo 120mg (n =154), or placebo (n =151), initially taking at least three or four doses before continued ascent	Prospective, double blind, randomized, placebo controlled trial	Lake Louise AMS score > or = 3 with headache and one other symptom. Secondary outcome measures: blood oxygen content, severity of syndrome (Lake Louise scores > or = 5), incidence of headache, and severity of headache.	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 acetazolamide (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).	Incomplete survey follow up. Ginkgo formulations may not be standardized.
Carlsten C, et al. 2004 Seattle, WA USA	11 patients taking acetazolamide 125 mg BID, 11 patients taking acetazolamide 250 mg BID, and 11 patients getting placebo BID over a 24-h period.	double-blind, randomized placebo-controlled clinical trial	Lake Louise AMS score and score trend	Nine of 32 subjects (28%) had symptom scoring diagnostic of AMS at 0 h. At 0 and 24 h (respectively), the mean Lake Louise scores were 1.73 and 1.09 for the 11 subjects receiving placebo, 1.45 and 1.36 for the 11 subjects receiving the 125-mg dose, and 2.7 and 0.6 for the 11 subjects receiving the 250-mg dose. The absolute change in these mean scores was not significant for placebo ($p = 0.21$) or the 125-mg dose ($p = 0.88$), but was significant for the 250-mg dose ($p = 0.008$). A comparison of a difference in decline in average AMS score over time showed a statistically significant decline for the 250-mg dosing group versus placebo ($p = 0.002$). The 250-mg dose of acetazolamide twice daily (but not 125 mg twice daily) was effective in inducing a significant decline in AMS symptoms over the 24-h period after arrival to 3630 m.	Small sample size. Measured AMS for only a 24 hour period. Unknown baseline characteristics or physical conditioning of the study participants. Acetazolamide should be given 12-24 hours prior to arriving at altitude and this was not done in this study.
Hussain MM, et al. 2003 Rawalpindi	Twenty four lowlander healthy male adults were sub grouped in a double blind fashion into four. Each subgroup (n=6) received placebo (multivitamin) or acetazolamide (250 mg) or dexamethasone (4 mg) or combined	Double blinded randomized placebo-controlled clinical trial	Arterial PO2, PCO2, SO2 and minute respiratory rate pH were measured. The pulmonary functions (FVC, %FEV1 PEF, FEF(25-75%) and MVV)	It is concluded that hyperventilation and increase in lung volumes are the adaptive pulmonary responses which help in improving levels of PaO2 and SaO2. The acetazolamide-dexamethasone prophylaxis appears beneficial in promoting pulmonary acclimatization during hypobaric hypoxia.	Low number of subjects in each treatment arm. Louise Lake AMS scores not used.

	regimen of the two drugs twice daily for 5 days commencing 24 hours before ascent. The volunteers reached the altitude of 4578m within a span of one day. The second group was acclimatized.				Vitamins may help prevent AMS and they were used as a placebo.
Chow T, et al. 2005 Loma Linda, CA USA	20 received acetazolamide; 17 received Ginkgo biloba, and 20 received placebo	Randomized, double-blind, placebo-controlled trial	Lake Louise AMS	The median score of the acetazolamide group was significantly lower than that of the placebo group (P=.01; effect size, 2; and 95% confidence interval [CI], 0 to 3), unlike that of the Ginkgo biloba group (P=.89; effect size, 0; and 95% CI, -2 to 2). Acute mountain sickness occurred less frequently in the acetazolamide group than in the placebo group (effect size, 30%; 95% CI, 61% to -15%), and the frequency of occurrence was similar between the Ginkgo biloba group and the placebo group (effect size, -5%; 95% CI, -37% to 28%). CONCLUSIONS: In this study, prophylactic acetazolamide therapy decreased the symptoms of AMS and trended toward reducing its incidence with no evidence of similar efficacy for Ginkgo biloba.	Small sample size. No all Ginko biloba samples are equally efficaciou s.
Wright AD, et al. 2004 UK	Study 1: 20 subjects randomized to receive medroxyprogesterone 30 mg or a placebo twice a day. Study 2: 24 subjects were randomly assigned to one of 4 groups: a placebo twice daily, medroxyprogesterone 30 mg twice daily, acetazolamide 250 mg plus a placebo twice daily, or acetazolamide 250 mg plus medroxyprogesterone 30 mg twice daily.	Two randomized placebo-controlled trials	AMS score and blood gas changes	Medroxyprogesterone improved peripheral oxygen saturations in both trials and improved PaO2 in combination with acetazolamide. Cerebral regional oxygen saturation was not altered by medroxyprogesterone. The reduction in symptom scores and in the extent of AMS was not significant in this limited study. Combined medroxyprogesterone and acetazolamide gave the best PaO2.	Small sample size especially in study #2. Few people developed AMS.
Ellsworth, AJ, et al. 1987 Seattle, WA USA	17 patients got 4mg dexamethasone every 8 hours, 15 patients got acetazolamide 250mg every 8 hours, and 14 patients got placebo	randomized, double-blind, placebo-controlled clinical trial	Environmental Symptoms Questionnaire and General High-Altitude Questionnaire	Dexamethasone group had significantly less AMS symptoms compared to placebo and with acetazolamide ($P< 0.05$). The acetazolamide group differed significantly from the other groups at low altitude in terms of nausea and tiredness (drug effect?) and a subgroup analysis of those on acetazolamide who did not experience drug effects showed that acetazolamide to be equal in efficacy to dexamethasone in preventing AMS symptoms.	Small sample size. Drug effects verses non-randomiza tion of subjects.
Bernhard, WN, et al. 1998 USA	13 patients got acetazolamide 500mg Q24 + dexamethasone 4mg Q12 and 13 patients got acetazolamide 500mg +	randomized, double-blind, placebo-controlled clinical trial	Environmental Symptoms Questionnaire	The acetazolamide + dexamethasone was more effective than acetazolamide alone in preventing the symptoms of AMS.	Small sample size

	placebo				

Comments:

Acetazolamide reduces the incidence of AMS compared to placebo. The side effects of acetazolamide include polyuria, paresthesias, and alters the taste sensation. Dexamethasone is also more effective than placebo in preventing AMS but 25% of patients experienced adverse effects (including depression) when withdrawing from the drug. There are no good (large) randomized clinical trials (RCT) comparing acetazolamide verses dexamethasone at preventing AMS.

There are no RCTs, one non-randomized trial, many observational studies, and consensus opinion which suggests that a slower ascent to altitude reduces the risks of AMS. There is one study which showed that there is no evidence of a difference in risk between men and women, or that previous episodes of altitude experience, load carried, or recent respiratory infection were risk factors for AMS. Having developed AMS at altitude previously puts you at risk for developing AMS again.
Although there are no RCTs evaluating the treatment of AMS, consensus opinion is that descending to a lower altitude and supplemental oxygen are the safest and most effective treatments for AMS. The widely held belief that the symptoms of AMS will resolve over a few days if there is no additional gain in altitude is not supported by any clinical trials. There are no good RCTs or systematic reviews on the effects of acetazolamide compared with placebo for treating people with established AMS. There is one RCT which showed that Dexamethasone was more effective than placebo at reducing mean AMS scores in people with symptoms of AMS. Furosemide and nifedipine may be effective in treating AMS, HACE, and HAPE. Inhaled beta-agonists may help prevent HAPE. Ginko biloba is probably not effective at preventing AMS.

Clinical bottom line: Acetazolamide 500-750mg/day (750mg/d is the most efficacious dose), starting 12-24 hours prior to arriving at altitude and continuing until at least maximal altitude gain, is effective at reducing the risk of AMS (NNT 2.9). Dexamethasone 2-4mg every 6-12 hours PO/IM/IV is also effective at preventing AMS but does not speed acclimatization (NNT 2.8). It is possible that combining acetazolamide and dexamethasone to prevent AMS is superior to either agent alone. Dexamethasone 4mg every 6 hours PO/IM/IV is also effective at treating the symptoms of AMS once they begin. Both acetazolamide and dexamethasone have unwanted side-effects. Ginko biloba is probably not effective, but antioxidant vitamins may be effective at preventing AMS.

References: see above